CENTERS FOR DISEASE CONTROL AND PREVENTION

NATIONAL IMMUNIZATION PROGRAM

RECORD OF THE MEETING OF THE

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

JUNE 19-20, 2002

Atlanta Marriott Century Center Hotel

Atlanta, Georgia

Table of Contents

ATTENDANCE

ACIP Members

Guthrie S. Birkhead, MD, MPH
Dennis A. Brooks, MD, MPH
Jaime DeSeda, MD
Celine I. Hanson, MD
Myron J. Levin, MD
John F. Modlin, MD
Paul R. Offit, MD
Margaret B. Rennels, MD
Natalie J. Smith, MD, MPH
Lucy S. Tompkins, MD, PhD
Bonnie M. Word, MD
Richard Zimmerman, MD

Ex-Officio Members

Centers for Disease Control and Prevention

Alison Mawle, MD, NCID
Walter Orenstein, MD, NIP
Dixie Snyder, MD (ACIP Executive Secretary)
Melinda Wharton, MD, NIP

Other Federal Agencies

Thomas Balbier, Health Research and Services Administration (HRSA)/National Vaccine Injury Compensation Program (NVICP)
James Cheek, Indian Health Services (IHS)
Benjamin Diniega, Department of Defense (DOD)
Geoffrey Evans, National Vaccine Injury Compensation Program (NVICP)
Randolph Graydon, Center for Medicare and Medicaid Services (CMS)
Carole Heilman, National Institute for Allergy and Infectious Diseases (NIAID)
Karen Midthun Food and Drug Administration (FDA)
Kristin Nichol, Department of Veterans' Affairs (DVA)
Eve Slater, Acting Director, National Vaccine Program Office (NVPO)

Liaison Representatives

Jon Abramson, American Academy of Pediatrics (AAP), Committee on Infectious Diseases (COID)
Robert Baltimore, AAP
Richard Clover, American Academy of Family Practitioners (AAFP)
Robert Daum, National Vaccine Advisory Committee; FDA Vaccine and Related Biological Products Advisory Committee
Jaime DeSeda, San Jorge Children's Hospital, San Juan, Puerto Rico
Stephan Foster, American Pharmaceutical Association
Eric France, American Association of Health Plans (AAHP)
Stanley Gall, American Academy of Obstetricians and Gynecologists (AAOG)
Luis Fernando Perez Glez, Council of Immunization Practices, SSA, Mexico
Rudolph Jackson, National Medical Association (NMA)
Stanley Katz, Infectious Disease Society of America (IDSA)
Martin Mahoney, American Academy of Family Practitioners (AAFP)

Victor Marchessault, National Advisory Committee on Immunization, Ontario, Canada
David Neumann, National Coalition for Adult Immunization (NCAI)
Kathleen Neuzil, American College of Physicians (ACP)
Georges Peter, National Vaccine Advisory Committee (NVAC)
David Salisbury, London Department of Health
William Shaffner, Infectious Disease Society of America (IDSA) and Guide for Adult Immunization
Jane Siegel, Hospital Infections Control and Prevention Advisory Committee (HICPAC)

Agency Staff

Department of Health and Human Services (DHHS)
Karen Becker, Office of Public Health Policy
Eve E. Slater, MD, Assistant Secretary of Health

Centers for Disease Control and Prevention (CDC)

National Center for Environmental Health (NCEH:) Debralee Esbit, Nicki Pesik

National Center for HIV, STD, and TB Prevention (NCHSTP): Allyn Nakashima, Karina Rupposelli

National Center for Infectious Diseases (NCID)

Anthony Albert	Keiji Fukuda	Alison Mawle
Loraine Alexander	Brenda Garza	Martin Meltzer
James Becher	K. Grass	Barbara Newhouse
Joseph Bresee	Rafael Harpaz	Janet Nicholl
Carolyn Bridges	James Hughes	Umen Parahar
Sarah Browning	Alan Janson	Michelle Pearson
Martin Cetron	Nino Khetsuriani	Lisa Rotz
R. Danielle Chikaran	Phyllis Kovarsky	Judy Schmidt
Joanne Cono	Rima Khabbaz	Don Sharp
Mary Cumberland	Charles LeBaron	Sarah Sibey
Robin Curtis	James LeDuc	Pamela Srivastava
Roz Dewart	Vladimir Loparev	Fran Walker
Debra Dotson	Jabina Lyson	Charles Vitek
Joseph Esposito	Bruce MacLachlan	
Maureen Fonseca	Eric Masa	

National Institute for Occupational Safety and Health N(IOSH:) Scott Deitchman

National Immunization Program (NIP):

Tameka Byrd	Bob Chen	Laura Erhart
Scott Campbell	Susan Chu	Sarah Foster
Christine Casey	Charmaine Coulen	Katie Fullerton
Deva R. Joseph	Edith Gary	Bill Gallo

John Glasser
Penina Haber
Pauline Harvey
Rita Helfand
Hayley Hughes
Sonya Hutchins
Marika Iwane
Michael Katz
Vanda Kelly
Laurie A. Johnson
Diane Kilgus
Kim Lane
Peng-Jun Lu
Joan Mahanes
Dean Mason
Mehran Massoudi
Elaine Miller
Gina Mootrey
John Moran
Pedro Moro
Arnaldo Muralles
Trudy Murphy
Diane Z-Ochoa
Ismael Ortega-Sanchez
Brian Pascual
Robert Perry
Carry Pickering
Susanne Pickering
Kelly Plots
Bette Pollard
Amy Pool
Maria Rangel
Susan Rey
Henry Roberts
Lance Rodewald
Marty Roper
Ben Schwartz
Jane Seward
Diane Simpson
Robert Singleton
Vishnu Priya-Sneller
Cheryl Stein
Ray Strikas
Charles Thompson
Amra Uzicanin
Angela Vargas
Sabrina Walton
Xiao Jun Wang
Michael Washington
Donna Weaver
Bruce Weniger
Skip Wolfe
Rachel Woodruff
Karen Wooten
Craig Wilkins
John X. Zhang
Laura Zimmerman

National Pharmaceutical Stockpile (NPS): Robert Snyder

National Vaccine Program Office (NVPO): Steve Sepe, Gregory Wallace

Office of the CDC Director: Sharon KD Hoskins

Office of General Counsel: Kevin Malone

Department of Defense DOD: R.D. Bradshaw, Charles Hoke, John D. Grabenstein, Scott Spratt

Food and Drug Administration (FDA): Karen Goldenthal, Cynthia Kleppinger, Dorothy Scott, Barbara Styrt

National Institutes of Health (NIH): *NIAID:* Sarah Landry, Barbara Mulach

Members of the public or presenters to the committee in attendance were:
Girtika Ahlija, ABC News
Steve Allred, getaflushot.com, Portland, OR
Larry Altman, New York Times, NYC, NY
B.F. Anthony, Biologics Consulting Group, Great Falls, VA
Susan Atlas, Cooney Waters Group, NYC, NY
Michele R. Bailey, American Social Health/CDC NIP, Research Triangle Park, NC
Denise Baker, NBC News, Atlanta, GA
Bryan Bechtel, Infectious Diseases in Children, Thorofare, NJ

Paul Blum, Acambis
Peter Bootsma, Royal Netherlands Embassy, Washington, D.C.
Dr. Luciana Borio, Johns Hopkins University
Judy Bowden, Fayetteville, GA
Greg Bowman, CNN, Atlanta, GA
Willis Boyd, WXIA TV, Atlanta, GA
Judy Brady, Henry Schein Company
Noelle Broadnax, NE Health District, Athens, GA
Daniel Brown, Washington Post, Washington, D.C.
Sgt. H.P. Brown, DeKalb County Police Department
Shawn Brown
Barbie Bushey, Northeast Haelth District, Watkinsville, GA
Pat Cannon, Wyeth, Newnan, GA
Carnns, Wall Street Journal, Atlanta, GA
CCJ Carpenter, Institute of Medicine (IOM), Providence, RI
Kevin Colley, Maxim Health Systems, Winter Park, FL
Dack Dalrymple, Dalrymple & Assoc/Pink Sheet, Washington, D.C.
Diana Davis, WSB TV
Jeffrey P. Davis, NVAC/Wisconsin Division of Public Health, Madison, WI
Joseph A. DiPisa, Biomedical Engineer, Wyckoff, NJ
Kris Ehresmann, Minnesota Department of Health, Minneapolis, MN
Craig Engesser, Wyeth, St. Davids, PA
Gary Evans, Bioterrorism Watch, Atlanta, GA
Gretchen Franklin, Health District 10, Athens, GA
Betsy Frazer, AQAF, Vestavia Hills, AL
Froeschle, Aventis Pasteur
Vincent Fulginiti, University of Arizona, Tucson, AZ
Diana Gaskins, GA Immunization Program, Atlanta, GA
Robert B. Giffin, IOM
Dahleen Gilanton, Chicago Tribune, Atlanta, GA
Ruth Gilmore, GA Immunization Program, Atlanta, GA
Jonathan Goldsmith, MD, Immune Deficiency Foundation, Towson, MD
Daniel Gordon, MD, Aventis Pasteur, Swiftwater, PA
Jesse Greene, South Carolina Department of Health and Environmental Control
Kenneth Guito, Aventis
Neal Halsey, Johns Hopkins University, Baltimore, MD
Claire Hannan, Association of State and Territorial Health Officers (ASTHO)
Celine Hanson, TDH, NYC, NY
Dr. Alan Hinman, Task Force for Child Survival, Decatur, GA
Dr. Robert Hirsch, MedImmun, Gaithersburg, MD
Joe Hirsch, Fox News Channel
Todd Hofmeister, Holland & Knight LLP, Atlanta, GA
Douglas Holtz-Eakin, White House Council of Economic Advisors, Washington, D.C.
Robert Hopkins, DynPort Vaccine Co., Frederick MD
Philip Hosbach, Aventis Pasteur

Michael Jester, NBC, Atlanta, GA
Virginia Johnson, DVC, Frederick, MD
Jan Jubilee, United Press International
Jay Karjewski, ABC News
Claudio Kelly, Merck Vaccine Division
John A. Kilgus, University of Virginia, Charlottesville, VA
Dr. Arlene King, Health Canada
Deborah, Kleijne, National Institute of Public Health, Bilthoven, Netherlands
Jim Knowles, NBC News, Atlanta, GA
Dr. Michael Lane, Atlanta, GA
Dr. Myron Levin, University of Colorado Health Science Center, Denver, CO
Dr. Daniel R. Lucey, Washington Hospital Center, Washington D.C.
Harold W. Lupton, Aventis Pasteur
Anita Manning, USA Today, Wilmington, DL
Ed McCarthy, CNN Radio, Atlanta, gA
Erin McClam, Associated Press, Atlanta, GA
Maryn McKenna, Atlanta Journal Constitution, Atlanta, GA
Paul McKinney, ASTM/University of Louisville, Louisville, KY
Dan McLaughlin, MedImmune
LuAnne McNichols, MN Department of Health, Minneapolis, MN
Dr. J. Donald Millar, Public Health Policy Advisory Board, Murrayville, GA
Nestor Molfins, Baxter Pharmaceuticals, Columbia, MD
Dr. Tom Monath Acambis, Inc., Cambridge, MA
Angela Moore, Children's Healthcare of Atlanta, Atlanta, GA
Wayne Morges, Baxter Healthcare, Columbia, MD
Marie Murray, Recorder, Atlanta, GA
David Neumann, National Coalition for Adult Immunization, Bethesda, MD
Peter L. Page, American Red Cross, Arlington, VA
Peter Paradiso, Wyeth Vaccine, West Henrietta, NY
Peter Paris, Cooney Waters Group, NYC, NY
Marsha Parker, Serologicals, Inc., Atlanta, GA
Bindi Patel, Merck & Co., West Point, PA
Diane Peterson, Immunization Action Coalition, St. Paul, MN
Cindy Philips, National Association of City and County Health Officers (NACCHO)
William Phillips, Atlanta, GA
Marc Pickard, WXIA-TV, Atlanta, GA
Stanley Plotkin, MD, Aventis Pasteur, Doylestown, PA
Zarnaaz Rauf, National Association of City and County Health Officers (NACCHO)
Delthia Ricks, Newsday, Melville, LI, NY
Zeil Rosenberg, American College of Preventive Medicine, Franklin Lakes, NJ
Rhonda Rowland, CNN, Atlanta, GA
Harry Samlet, WXIA TV, Atlanta,GA
Stella Sanford, Atlanta, GA
W. Lewis Schewistzer, CBS Atlanta, Atlanta, GA
Joel Schoenfeld, UNIVEC, Woodbury, NY

Dr. Alan J. Sievert, East Metro Health District, Lawrenceville, GA
Paul Simao, Reuters News Services, Atlanta, GA
Bob Sirkin, CBS Radio Roswell, GA
Barbara A. Slade, MD, Serologicals, Inc., Decatur, GA
Ben Sloat, GA Division of Public Health, Atlanta, GA
Gregory Smith, AP
Parker Smith, PCS Photo
Dr. Dean Smith, Health Canada
Karen H. Smith, Athens Regional Medical Center, Athens, GA
Ron St. John, Health Canada, Ottawa, ON, Canada
Gary Stance
Stoddard, MedImmune
Dr. Kathleen Stratton, IOM
Stacy Stuerke, Merck
Dr. L. J. Tan, American Medical Association
William Tell, Advisory Board Company, Washington, D.C.
Sherri Tenpenny, National Vaccine Information Center, Strongsville, OH
Dirk E. Tevwen, Aventis Pasteur, Lyon, France
Ed Thompson, ASTHO/Mississippi State Department of Health
Eric Tischler, Aventis Pasteur
Karen Townsend, GA Chapter, AAP
Miriam E. Tucker, Pediatric News/Family Practice News, Rockville, MD
Susan Vaunsen, ALG, Norcross, GA
Tom Vernon, MD, Merck Vaccine Division, West Point, PA
Tom Waites, BioPort, Inc, Lansing, MI
Gary Wallach, Research Triangle Park, NC
Deborah Wexler, Immunization Action Coalition, St. Paul, MN
Kathi Williams, National Vaccine Information Center, Vienna, VA
Matthew Williams, Flu Central, Doraville, GA
Mary Alice Woody, Joint Vaccine Acquisition Program, Frederick, MD
Steve Wright, Maxim Healthcare
Arthur Yancey, National Association of EMS Physicians, Lenexa, KS
Greg Yoder, Merck & Co.
John Zahradnik, Aventis Pasteur
Thomas Zink, GSK Vaccine, Philadelphia, PA

CENTERS FOR DISEASE CONTROL AND PREVENTION
NATIONAL IMMUNIZATION PROGRAM
ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

MINUTES OF THE MEETING
JUNE 19-20, 2002

JUNE 19, 2002

Opening Comments
A meeting of the Advisory Committee on Immunization Practices (ACIP) was convened by the Centers for Disease Control and Prevention's (CDC) National Immunization Program (NIP) at the Atlanta Marriott Century Center Hotel in Atlanta, Georgia, on June 19-20, 2002. The meeting agenda (posted on CDC's Website, http://www.cdc.gov/nip/) included four hours of time devoted to public comment on use of smallpox vaccine. The meeting was convened by ACIP Chairmen, Dr. John Modlin at 8:30 a.m.

ACIP Executive Secretary Dr. Dixie Snider made several announcements:
- New member Dr. Celine Hanson, of the Texas Department of Health, was welcomed.
- Certificates of appreciation were awarded to Dr. Paul Offit and Dr. Peggy Rennels for their service to the Committee.
- The next ACIP meetings will be on October 16-17, 2002 and in 2003 on February 26-27, June 18-19, and October 15-16.
- The updated interim ACIP policies and procedures were in the members' meeting books.

Dr. Modlin called for introductions of those present (see preceding pages) and explained the ACIP policy on conflict of interest. Members stating the latter may participate in all meeting discussions, but may not vote on any issue related to that conflict, nor may they introduce or second resolutions pertaining to the Vaccines for Children (VFC) program. Members reporting potential conflicts were:
- Dr. Richard Clover: Potential conflicts of interest with Wyeth Lederle, Glaxo Smith-Kline, Merck, Pfizer and Bayer.
- Dr. Myron Levin: conducts research with Merck and with SmithKlineBeecham.
- Dr. Paul Offit: is co-holder of a patent on a bovine-reassortant rotavirus rotavirus vaccine and consults on its development with Merck & Company.
- Dr. Rennels: conducted vaccine trials with Wyeth, Lederle, Merck, Glaxo Smith-Kline and Aventis Pasteur.

Members Robert Belshe and John B. Salamone were absent.

Meeting Background. Dr. Modlin recalled DHHS' request, with some urgency, that ACIP reconsider its current smallpox statement. The entire agenda of this meeting was

devoted to this topic, to ensure adequate time for presentation of the background information that is normally presented over two or more meetings. The current ACIP recommendation for smallpox vaccination, issued in June 2001, applies only to those working with non-highly attenuated orthopox viruses. There is no indication the threat has increased since the 9/11 attacks, but the perception of risk has, and it is known that the U.S. is vulnerable to enemies with such an attack capability. These concerns about risk are credible and need to be taken seriously, although better data on the actual risk-benefit would be desirable. DHHS studies show that the current Dryvax® vaccine can be expanded 5- to 10-fold through dilution, but it is still formulated in 100 dose vials, implying wastage. In addition, the imminent availability of adequate vaccine supplies through the Acam2000 release drives the need for timely decisions. As a result, a joint NVAC/ACIP smallpox working group was formed. It members and the CDC/NIP staff who support it were listed, and its work time line was outlined.

Charge to the Committee. Dr. Snider asked the Committee to discuss three critical questions of focus at this meeting, to formulate a recommendation for CDC to then be transmitted to the DHHS Secretary. If the recommendation is made to expand vaccination further, significant issues of implementation will have to be discussed, including the oversight and monitoring of such an effort.

Discussion of Questions

Dr. Joel Kuritsky provided the questions to be addressed. Shortly after the 2001 anthrax attacks, CDC formed 20 multi-disciplinary smallpox response teams of ten individuals each; published the interim smallpox response plan and guidelines in November 2001; and in January 2002, published the rash algorithm now in use. He reiterated the recommendation for smallpox vaccination published in the *MMWR*, the relevant factors to consider, and the seven assumptions for the development of vaccination policy options. He then reviewed the options relevant to each question.

Pre-attack considerations:

Question 1: With no known cases of smallpox worldwide, should there be any change in the current recommendation for not vaccinating persons in the general population before there is a confirmed smallpox case or a confirmed bioterrorism attack using smallpox?

1. Option 1: There should be no changes in the current recommendation.
2. Option 2: Continue current recommendations for not vaccinating in the general population in the absence of a bioterrorist smallpox attack, but allow permissive or voluntary use of the vaccine for persons in the general population who desire to be vaccinated despite the recommendation.
3. Option 3: There is no positive or negative recommendation. The Committee is neutral but recommends that vaccine be available for individual choice;
4. Option 4: Routine vaccination is recommended for those who wish it.

Question 2: In addition to laboratory workers who work with viruses related to smallpox, are there other individuals in specific occupational groups who should be vaccinated to enhance smallpox preparedness? If so, what guidelines should be used to determine which individuals should be vaccinated before there is a confirmed smallpox case or a confirmed bioterrorism attack using smallpox?

1. Option 1: No change in the current recommendation.
2. Option 2: Vaccination of persons pre-designated by appropriate bioterrorism and public heath authorities to have direct contact or investigation of the initial cases of smallpox (e.g., clinical staff at selected healthcare facilities, smallpox response teams at the federal, state and local level who would be called upon to investigate smallpox cases, and contain outbreaks).
3. Option 3: Extend Option 2 to include smallpox vaccination of pre-designated "essential" medical and non-medical service personnel (e.g., additional healthcare workers and first responders).

The result of the options related to these two scenarios range from vaccination of hundreds to millions of persons.

Post-attack, confirmed smallpox case/attack considerations:

Question 3: Should there be a change in the current recommendation that surveillance and containment ("ring vaccination") will be the primary strategy for the control of smallpox in the event of a confirmed smallpox outbreak or a confirmed bioterrorism attack using smallpox?

1. Option 1: Surveillance and containment ("ring vaccination") as the primary strategy, with the ring as large as desired.
2. Option 2: Supplement Option 1 with vaccination of medical, health, law enforcement and other personnel who would assist in responding, managing, and investigating the outbreak or attack. If so, what guidelines should be used to determine which individuals should be vaccinated before there is a confirmed smallpox case or a confirmed bioterrorism attack using smallpox? (The Bureau of Labor Statistics estimates a total of ~11.4 million Americans employed in health services, including allied health.)
3. Option 3: Conduct surveillance and containment and vaccinate those in the community(ies) who so desire.
4. Option 4: Conduct surveillance and containment *and* do mass vaccination of the U.S. population (estimated at 280 million doses) as concurrent strategies for the control and containment of smallpox.

PRESENTATIONS

Clinical/Diagnostic and Epidemiological Features of Smallpox

Dr. Walter Orenstein reported that the distinctive clinical features of smallpox in the pustular phase make diagnosis likely. Smallpox is transmitted generally through large droplets that fall quickly to the ground. It does not spread rapidly like measles or

pertussis, and most transmission is from significant face-to-face contact. Normally, by the time smallpox is transmissible, the patient is extremely ill and not ambulatory, although there are exceptions to the rule. Photos of classic variola major showed its rash as generally distributed over the body, but less so on the trunk. The lesions are deep and brawny, not superficial like those of chicken pox. The incubation period is about 12 days in a range of 7-17 days, during which the patient is not infectious. Fever emerges for 2-4 days, then the rash. The lesions are always in the same stage of development. It is in the first few days of this period, when patients are contagious, that smallpox is difficult to diagnose.

There are several types of smallpox:

1. With no rash (variola *sine eruptione* – this plays no role in transmission).
2. A modified rash (among people with some pre-existing immunity, this may progress more rapidly and they may shed less virus, but the patient is more mobile and so exposes more people. Very few Americans under age 30 would be in this category).
3. Types of variola major ("normal smallpox") include rashes that are discrete or semi-confluent, or confluent.
4. The more atypical, very severe and highly contagious forms are flat smallpox and early- and late-smallpox. Rather than progressing, the lesions of flat smallpox appear as one lesion over the body, resembling a burn. The ~30% mortality rate for this form is higher than the average of the other smallpox. Hemorrhagic smallpox resembles hemorrhagic fever in its early stages. It accounts for 3% of cases and is usually detected when the next generation of transmission appears.

Viral shedding appears to increase with greater disease severity. Lab confirmation is possible through rapid diagnostic testing with nucleic acid-based testing, specimen culture, electron microscopy, and serologic testing. CDC can turn around test results in about eight hours.

The conclusions drawn about smallpox transmission were:

- The airborne droplet face-to-face nasal pharyngeal droplet transmission from a distance of 6-7 feet, should be interruptible with droplet mask protection (N95), except for cough and sneeze transmission. The latter is unusual in classic smallpox, however, as are the rare airborne outbreaks where the virus spread over long distances.
- There is no carrier state.
- Rarely, transmission occurs by fomites in bedclothes, linens and blankets. But these normally do not survive long in the environment and the virus in scabs is generally too enmeshed in the fibrous carrier to transmit. Smallpox is not transmitted by food or water.

Factors influencing the spread of smallpox include:

- Temperature: aerosols have higher viability with lower temperatures; an attack would be better facilitated in winter or spring.
- Humidity: aerosols have a higher viability with lower humidity (accounting for its seasonal character).
- Intensity and duration of contact (higher infection rate for contacts of $\geq$7 days duration).

- Contagious period when exposed: the highest viral titers are cultured in the early stages of rash in the first weeks of illness. There is little virus in the oral pharynx and more on the skin late in the second week.
- Population density: greater potential for spread with more people in contact.
- Coughing/sneezing are more likely to disseminate the virus by the aerosol route.

Infectiousness. The D.A. Henderson review article (*JAMA* 1999) describes the patient as feeling quite ill in the prodrome stage, from the rash onset to 14 days. S/he feels better thereafter, but remains very toxic to about day 26, when death may occur. A graph of this progression is attached to this document (Attachment #2).

How contagious smallpox is, is a matter of debate. Mathematical modelers developed the concept of R-zero (R^0), the reproduction number or number of secondary cases that would be expected *on average* with one introduction of a virus into a completely susceptible population. The 1993 analysis by Paul Fine (*Epid Rev;* 15:265-302) demonstrated that smallpox, with an R^0 value of 4.7 or less since 1800, is less contagious than measles, for example. Measles' infectiousness, with great transmission in the prodrome, defeated use of the ring strategy as a control measure. Smallpox is more comparable to polio, diphtheria, mumps, or rubella. Currently, measles immunization levels in the U.S. approach the herd immunity threshold.

However, 2001 data demonstrate that the greatest threat posed by smallpox exists in the hospital setting, where the R^0 almost approaches the measles range, moving up to $R^{10\text{-}12}$ (Ganney and Leach, *Nature*, December 2001). The R^0 of smallpox outbreaks have followed Fine's algorithm, except for the Kosovo and European outbreaks in 1972 and 1958-1973, respectively, when the R^0 exceeded 5.0, and in hospitals increased to $R^{10\text{-}12}$.

Smallpox transmission. Dr. Orenstein shared examples of smallpox transmission within a single compound in Nigeria and Cameroon. The interval in the compound between onset of symptoms in the index case and the onset of symptoms in the last case demonstrated that it did not spread rapidly. Fenner *et al*, in *Smallpox and its Eradication* (pp 200) reported that the secondary attack rate for smallpox among unvaccinated persons was 36-47% in five studies and 73-88% in three, averaging a 58% secondary attack rate. This supports the conclusion of lower smallpox contagion than other disease such as measles.

Degree of contact. The Mack study data, which included smallpox importation to Europe from 1950-1971, showed that 93% of cases were predictable. About 83% of importations could be traced to hospital or work-related transmission (e.g., laundry workers dealing with bedding) or family/intimate contacts. Only 10% of cases were a result of casual transmission, and only 7% were unpredictable cases. The general predictability, according to contact with smallpox, was such that 41% among hospital staff and family and 59% among hospital clientele developed smallpox from contacts, but 91% of the latter were in-patients (*J Infec Dis*, 1972, 125:161-169). Source tracing of patients in India's last smallpox outbreaks paralleled that predictability.

Smallpox Vaccine Performance: Efficacy, Effectiveness and Vaccination Strategies

Dr. Harold Margolis, Senior Advisor on Smallpox to the CDC director, discussed pre-exposure immunization, long term effectiveness, and adverse effects.

Estimates of vaccination efficacy reflect three limitations: 1) There has been little published in the last two decades on immune response to smallpox; 2) most data are not from controlled clinical trials and most conclusions are derived from clinical and epidemiological studies done ≥30 years ago; nor 3) are there any good animal models of smallpox from which to extrapolate outcomes.

Pre-exposure immunization. In the absence of controlled clinical trials, protection has been estimated from comparisons of secondary attack rates among vaccinated and unvaccinated family contacts of cases. Vaccination status was determined by the presence of a scar, without accounting for vaccine potency or that the scar may be secondary to a skin infection rather than a vaccine take; and there was no indication of "on-time" vaccination to determine the person's exposure status relative to the scarring.

The data by Fenner *et al* (WHO 1988, p591) are most recent on the effect of pre-exposure vaccination. They show high efficacy ranging from 91%-94%, but that also depended on the kind of smallpox developed. Their case fatality rate for discrete smallpox was 10%, but ≥90% for flat or hemorrhagic smallpox. Fatality with vaccination was low for discrete smallpox, but the vaccine was not protective for hemorrhagic smallpox, a rare complication. Other observations indicate that the latter involves a host response rather than a virologic determinant.

Post-exposure protection. Vaccine effectiveness studies suggest protection. The vaccination status of contacts by Fenner (*Smallpox and its Eradication*, p591) showed secondary attack rates of 21% to 96% for those never vaccinated. However, the time period post-exposure was not delineated in these studies to indicate the window of efficacy. Vaccine efficacy was demonstrated in a ≤91% reduction of secondary attack rates for those with discrete smallpox, compared to unvaccinated contacts. The lowest disease rates were among persons vaccinated <7 days post-exposure, and the disease was generally less severe (modified type) in those persons. While it is difficult to define the period of highest efficacy from available data, earlier is probably better as with other post-exposure immunization. It at least is clear that ensuing disease is less severe.

Duration of Vaccine Protection involves several determinants, such as antibody and persistence of neutralizing antibody, and immune memory in various CTL compartments. The data on long-term persistence of cell mediated immune memory to vaccinia, as reported by several studies, were reviewed.
1989 Israeli military personnel studies measured post-vaccination antibody persistence. The pre-vaccination titers of 18 year-old recruits (who were vaccinated at age 1 and 8 years and then revaccinated on entry to the military) rose from 18.5 to 75 after revaccination with the Elstree strain (Lister) vaccine. The antibody levels of reservists vaccinated at 0, 8, 18 years of age and not revaccinated since had dropped, but persisted, as measured by antibodies and plaque reduction. Most were immunized by jet injection, but some were by scarification with a

bifurcated needle. (Baruch *et al*, *JID*).

Studies of immune memory in various CTL compartments were all done with live vaccinia (not variola) targets. Memory cells appear to be present for ~20-30 years post-vaccination, although at low levels. Both cytotoxic T lymphocytes (CTL) and antibody are needed for effective protection, but that combination has not been studied. Dr. Margolis reviewed several epidemiological studies. Data from a Liverpool, England, study of infant smallpox immunization in 1902-03 (Hanna, W, 1913) demonstrated lower mortality and sustained protection among persons vaccinated 20-30 years earlier, versus high death rates among unimmunized patients. However, the vaccinated cohort also may have had some naturally-acquired immunity that was boosted by the vaccination. However, the Mack data (*J Infect Dis* 1972;125:161-9) of European cases introduced from Asia (1950-1971) also suggest a modest but present persistence of immunity among persons who were less likely to have had naturally acquired immunity, with similar protection remaining from previous vaccinations. Smallpox was not endemic, so people were probably not getting naturally-occurring boosts. And some studies of persons who had previous smallpox, or who had a primary take from vaccination at any point from 5-10 years after having had smallpox, reflected a high rate of primary takes after vaccination with vaccinia.

So, while there are little data to define the identity or determinants of the best markers of long-term immunity, there is evidence of persistence of long-term antibody in cell-mediated immunity (CMI). Pre-exposure vaccination provides protection, but while post-exposure vaccination offers a wide range of protection and is protective against death long-term, the effect on the disease is hard to predict. While the vaccine probably does not prevent disease, it may modify it, and it definitely reduces death.

Characteristics of smallpox. Smallpox is a clinically evident disease. There is no subclinical illness or carrier state; transmission does not occur during the prodrome, and maximum transmission occurs at a time of rash illness. The vast majority of cases can be traced to face-to-face contact. Systemic signs and symptoms associated with smallpox vaccination include muscle aches, fatigue, a fever ($\geq 100^0$F) peaking at ~7-9 days post-vaccination, moderate or severe localized pain, and often disturbing itching at the injection site. Interruption of work or normal daily routine was likely for ~30% in the Frey and Belshe study (*NEJM*, 2002, 346:1265-74). Some primary vaccine takes were perceived to be cellulitis with aggressive induration and erythema at ~10 days, which were treated with antibiotics. Dilution studies showed reduced erythema and diameter of induration, but an increase of local satellite lesion sites.
Dr. Margolis summarized that smallpox vaccination given pre-exposure provides high levels of protection. There appears to be long-term protection of varying degrees, most easily measured in lowered case fatality rates. However, smallpox vaccination causes local and systemic adverse events.

Studies/Overview; Dr. T. Mack
Dr. Thomas Mack, of the University of Southern California School of Medicine, has focused in the past 40 years on population based investigations of smallpox outbreaks of all sizes, as well as

individual cases that do not come to the authorities' attention.

In his *Pakistan* study, over 25% of the population were unvaccinated, mostly living in villages of 1000-5000 people, who lived in 20-100 crowded compounds of 5-30 persons each. Any given village would have imported smallpox once every 15 years; medical or public health care was virtually nonexistent to provide any intervention. The *European* outbreaks were in susceptible populations (lesser communication, lower standard of living than today), whose physicians were unfamiliar with the disease. These situations made the propensity for spread greater than it would be in the U.S. today.

Regarding vaccinia, Dr. Mack emphasized the importance of VIG to the ACIP's deliberations. Without it, any extensive vaccination program would be extremely dangerous.

Smallpox studies demonstrate that vaccination take is an important determinant of disease severity, regardless of the interval since the case occurred. The trade-off is with smallpox, whose case fatality rate is 10-15% among adults. Transmission occurs within social circles, not within the population at large, and subgroups cannot be sustained. Even in the absence of a smallpox eradication program, Dr. Mack suspected that the disease would have died out anyway, just over a longer period. The outcomes of smallpox are essentially untreatable permanent scars on about half of survivors. But a few features facilitate control. Dr. Mack shared photos of a woman and man at three 3 days and then of the woman at 7 days. Both would be hard to diagnose with experience with smallpox. But at 7 days, her pustules were fully evident, and the man died of confluent smallpox that could not have been detected from his early appearance.

In 27% of the cases in India where there was no care provided, there also was no transmission at all. Another 37% reflected only one generation, but the mean length of the outbreaks were 6 weeks (3 generations). Dr. Mack presented data on disease spread measured by living arrangements (density increases) and by humidity.

He then outlined the probable attributes of terrorist introduction of smallpox:

1. A small number of cases, probably <10. Suicide dissemination is probably unlikely due to the severity of the disease. Since airborne spread is very inefficient, the release would probably be done in an enclosed place such as an airplane, resulting in a substantial number of cases, but they would share common experiences to allow tracking.
2. Cases would be florid in the immunosusceptible population of the U.S.
3. People would be aware of exposure after initial diagnosis; dissemination from the initial cases would probably be relatively limited.

The key to control of any introduction is surveillance, and initial recognition is the most important factor. Identification of all cases and contacts of known and probable cases would ensue, and prevention of admission to hospitals. Separate facilities would be opened, and likely contacts would be vaccinated.

Initial recognition and awareness of the possibility of disease is more important than substantive

knowledge of differential diagnosis. Dissemination of large photos of the classical smallpox presentation will make ER personnel aware. Early diagnosis will remain difficult, but it will be clear after a few days, and subsequent cases will be identified. Some may be missed, but not many.

Contact identification and follow up. The more cases, the more personnel will be needed. The example of the fire fighter model should be followed to address a smallpox outbreak, to prepare every locality to address it and to gather together as needed. The more public the exposure, the more staff will be needed. The availability of protected personnel is key (e.g., field epidemiologists, lab technologists, care providers). Those already vaccinated would be alerted, with priority given to older and foreign physicians. Multi-locality and federal cooperation will be advantageous.

Prevent admission to hospital. The most important determinant of the eventual number of cases depends entirely on the state of alertness and familiarity with the possibility of the syndrome. A dedicated facility need not be large; it would be better small and agreed upon than large and contentious.

Populations requiring separate vaccination policies include:

1. Those in contact with cases should be vaccinated immediately; passive immunization and chemotherapy should be explored.
2. Those expected to implement control.
3. Those known exposed to a case or an exposed person. After screening for those at risk of complications, with VIG available, provide post-exposure vaccination. This provides imperfect protection, but may reduce disease severity. Data of the Pakistani and Indian attack rates by vaccination state indicated evidence of effectiveness, although the numbers may or may not be statistically significant.
4. Those not so exposed but at risk of workplace exposure (e.g., physicians and nurses). Dr. Mack discouraged this, due to their unlikelihood of contact with the few number of cases, and because of the difficulty of limiting vaccination to certain groups. This could open the door to mass vaccination of people who may not have carefully considered the risks.
5. Members of the community at large. Similarly, this group has negligible risk from smallpox introduction and a substantial risk from vaccination. Identified contacts will still need to be vaccinated; personnel and resources will be needed for surveillance; and protection is not maintained by vaccination – communities will have to be re-vaccinated. Finally, the necessary informed consent will have to state that the risks exceed the benefits.

Dr. Mack stated his belief that endemic smallpox will never return. It disappeared from the U.S., Europe and other developed countries due to economic development. He was certain that it would not be sustained even in the event of several importations. For these reasons, knowing of a subway exposure in New York City, for example, he would finance the preparation of field workers than prophylactic mass vaccination. The first unnecessary death from a vaccination complication would ensure more smallpox transmission, because those needing the vaccination

under the right circumstance would refuse it. The presence of partial herd immunity also would tempt complacency.

Therefore, Dr. Mack provided his responses to the three questions:
1. Option 1 (no mass prophylactic vaccination).
2. Option 2 (vaccinate only specially selected federal and local response teams [field, lab, health care]) after appropriate screening). He emphasized the inclusion of local staff, since CDC cannot respond quickly enough, and the difference of post-exposure vaccination on day 2-3 or day 6-7 may be important.
3. Conduct surveillance; vaccination is a subsidiary consideration to surveillance.

Ring Containment and Policy, Dr. M. Lane

Dr. Michael Lane, a consultant to the NIP on smallpox, outlined the genesis of the policy change from mass vaccination to isolation, the elements of the policy, and the likelihood of surveillance and ring containment's success.

The characteristics of smallpox which led to control and eradication were the ability to identify cases, the relatively slow movement of the disease, the effectiveness of pre-exposure vaccination and, most likely, early post-exposure vaccination. The WHO noted in 1966 that the mass vaccination policies of the 1950s were not optimal, since there was no way to know what pockets were missed, and recommended that coverage surveys be included. Their policy changed in 1968 to surveillance and containment, a policy change that was supported by experience:

1967 West Africa smallpox outbreak control field work. Spread of smallpox is very slow; virtually all cases came from prolonged (≥1 day or longer) face-to-face intimate contact. Small numbers (e.g., <200 people) were capable of sustaining transmission for 4-5 generations, demonstrating smallpox' slow spread. Marked seasonality was evident; <1 case was spread per index case in the seasonal downswing. The failure of mass vaccination was demonstrated in Foege's mass vaccination in Nigeria, in which an 88% effective coverage rate was followed by a focal outbreak four weeks later.

Strategies for smallpox eradication over time ranged from mass vaccination in the 1950s to rash surveillance in 1975. Ring vaccination around multiple cases in multiple places was the strategy proven effective in smallpox eradication. This process finds cases, provides immunity around each case, and provides immunity around the contacts of the case. Decision are made at a local level on how extensive the second ring should be. Surveillance and containment (ring vaccination) searches for cases and provides a ring of immunity around each case, isolates the cases and contacts, and provides immunity around the contacts.

Smallpox eradication in west and central Africa was described. When corrected for under-reporting, data indicate an estimated 200,000-400,000 cases occurred annually among ~20 countries. Cases continued to occur among unvaccinated persons despite mass vaccination campaigns. Surveillance was initially thought to be most useful in the maintenance phase of

program, after mass vaccination, but accumulating evidence suggested that surveillance and containment were still more effective than mass vaccination. A chart of the search/containment of reported smallpox cases in west and central Africa from 1968-69 showed a rapid decline of cases reported versus those expected after the initiation of surveillance/containment. This reflected similar experience in other areas such as India and Pakistan.

Exposure factors for smallpox in West Pakistan, 1968-70 were studied (Heiner *et al*, *Amer J. Epidemiol* 1971; 91:316-326) in six villages in Punjab province. Index smallpox cases (the first in a compound) and contacts (any person regularly sleeping in the same house or compound as the index case) were studied for two exposure types: 1) constant (sleeping in the same house and remaining there during the day); and 2) daily (left the house or compound during the day). Disease rates were only slightly higher by residence status (living in same house versus the same compound), but differed radically by pattern of exposure (81 cases with constant exposure versus 10 with daily exposure) and duration of exposure (91 case $\geq$7 days versus none $\leq$7 days).

The *operational aspects of surveillance/containment* include intense surveillance for case detection and delineation of functional and geographic boundaries around case(s) or outbreaks. But outbreak control activities must be given first priority, including communication.

Dr. Lane provided several reasons that the surveillance/contact vaccination strategy in the U.S. would succeed as opposed to less successful experiences, specifically in Asian and African villages.

1. Better U.S. media communication and cultural acceptance of case identification would allow cases to be identified earlier to rigorously isolate patients, and N95 masks are available. Identification of contacts would be similarly aided by media assistance, and vaccination of contacts will be easier than in Asia and Africa, where there is mistrust of government and poor vaccination methods. In the U.S., the public will demand vaccination.
2. Surveillance of contacts for fever is very labor intensive in Africa, but is facilitated in the U.S. by the Visiting Nurse Association (VNA), self-reporting, and the use of phone and e-mail.
3. On the other hand, the ease of identifying second ring members in Africa and Asia, due to close-knit communities, might be harder in the U.S. Media cooperation and considerable personnel may be required.
4. However, once identified, communication with second ring members is facilitated by modern communications methods in the U.S. The relative isolation of second ring members in Asia/Africa, who may have been unaware they were sick, challenged this, particularly when multiple villages were involved. It is unknown, in the U.S., how compliant second ring members would be.

Clinical Presentation/Treatment, Vaccinia Adverse Events; Dr. V. Fulginiti

Dr. Vincent Fulginiti, Professor Emeritus in Pediatrics of the University of Arizona and the University of Colorado, outlined for the workgroup the clinical presentation and treatment of the adverse events of vaccinia smallpox. His presentation was based on his work at the Center for

Consultation with Dr. Henry Kemp, a pioneer of smallpox immunization from the 1950s-1970s, at the University of Colorado Health Science Center. He specified that much of this information was from an era of much less immunologic knowledge. In fact, much of the current knowledge is based on the complications of smallpox vaccination, particularly progressive vaccinia.

Intense inflammatory response around the primary vaccination is now known to be due to t-lymphocytes around the vaccination site. The multiple complications of smallpox vaccination include noninfectious rashes, infectious complications (bacterial and viral), post-vaccinia encephalitis which is probably immunologic in origin, and other temporally-connected lesions that occur with any vaccination. Their relationship of complications to the vaccine is problematic; most are probably unrelated, although a temporal relationship has been shown for osteomyelitis.

Non-specific, non-infectious rashes such as *Erythema multiforme* manifests in various forms. It is common 8-14 days post-primary vaccination and is frightening in appearance to patients, but is benign except for the rare Stevens-Johnson Syndrome. Forms are macular rash, maculopapular, and occasionally vesicular rash, and urticaria. The lesions are very puritic. Most of the researchers thought these to be allergic reactions, but allergic and toxic properties of the virus could not be distinguished.

- Diagnosis is by clinical appearance and temporary association with the vaccine. Consultation to rule out other skin conditions is rarely required.
- Treatment is symptomatic; usually with antihistamines, but SJS may require steroids locally and systemically.

Bacterial superinfection. Previously, tetanus, syphilis and enteric bacterial infections were complicating infections, but staph and strep now predominate. Previously totally occlusive dressings caused enhanced infection rates.

- Diagnosis: For staph, a vesicular border and a clearing center; for strep, lesions 'heaped up" one upon the other. Occlusive dressings can aggravate this.
- Treatment: Responds rapidly/completely to prompt appropriate antimicrobial therapy.

Inadvertent accidental inoculation of self by oral (e.g., by children) or intramuscular (IM) injection route (no adverse effects without oral injury from vaccine instrument injury in mouth), or autoinoculation or from a vaccinee. Any part of the body can be affected, but the most serious sites are from inoculation of the cornea from keratitis, burns, and eczema vaccinatum (EV). The latter can have a 30% mortality rate if untreated, but none if treated with VIG. Predisposal to infection comes from traumatic/surgical wound inoculation and may occur from dermal infection. Mucosal inoculation is possible. Accidental inoculation is common in very young infants/children (transfer from hand to skin/mucosa, eye rubbing, predisposes them to periorbital/corneal lesions), whose caretakers are also at risk. Bathing can also result in autoinoculation. Any disrupted skin can provide entry, including diaper rash and acne.

- Diagnosis: is by clinical appearance; the lesions are identical to the original vaccination site. Some confusion is possible with ocular herpes and wound/post-surgical lesions. For these, a contact history will be important. Viral tests occasionally are indicated.

- Treatment: is 0.6 mg/kg VIG for most lesions, perhaps 1-2 mg/kg; and 1-5 mg/kg for EV (although ≤10 mg/kg has been used for huge lesions); and topical antivirals for eye infection. Use of *VIG is avoided,* which can prompt an Ag/Ab reaction in the eye. Thiosemicarbazone also was sometimes used, being the only antiviral available in those days. That is not true now, and there are little data on which to judge efficacy.

Congenital vaccinia is rare, posing the greatest danger from vaccinating pregnant susceptible women in the third trimester. No congenital anomalies were linked to maternal vaccination.

Generalized vaccinia is often benign, despite it appearance, but it can progress. It differs from EV and progressive vaccinia. Multiple lesions look "normal" and occur in healthy individuals and are presumably bloodborne. They are usually self-limited, but are rarely recurrent every 4-6 weeks up to one year. Primary is normal and self-limited.

- Diagnosis: is by the characteristic clinical presentation; viral isolation or identification is done as needed; immunologic studies are warranted with current knowledge of range of defects. Some children have been seen with repeated episodes, indicating that there may be some subtle immune defect.
- Treatment: is with 0.6 mg/kg VIG repeated as needed with repeat episodes. Antivirals can be considered.

Progressive vaccinia (vaccinia necrosum, vaccinia gangrenosa) is the disease of most concern. It is a progressive enlargement of the primary infection with viremic spread to other parts of the body, each lesion expanding without limitation. It occurs primarily in those with cell-mediated immunodeficiencies, but a few cases have been seen among hypogammaglobulinemic patients. It was fatal in most cases, but a few patients survived after amputation and therapy. A larger population is susceptible today than in the past, mostly children and children with T-cell deficiency (AIDS patients, people treated with cortisone and anti-inflammatories).

- Diagnosis: This occurs after a normal vaccination with lesions with no inflammation, but progresses in size without limitation. Virologic tests and genetic testing are conducted and family history is taken; immunologic assessment is critical. Cell transfer resulted in GBS; caution is required in this regard.
- Treatment: was by VIG and plasma, exchange transfusion; antiviral therapy (but IUDR was ineffective), then with Thiosemic arbazone (perhaps now Cidofovir); cell transfer (GVH resulted); and genetic testing. Perhaps gene therapy will be done in future. In one described case, the similarity was noted to Runts Disease in mice, the forerunner of graft versus host disease. Some thought a new immunologic disease had been discovered, but Nezeloff had described this previously. After treatment with VIG, surgery was performed to excise the lesions, followed by grafting of skin donated by the mother and further treatment with antibiotics. The child recovered.

Post vaccination encephalitis is rare (1:100,000-500,000 vaccinations, although a more genetically homogeneous study population Dutch recruits had a prevalence of 1:50,000). Outcomes vary in severity and prognosis, from mild and self-limited to progressive and fatal. There is some question if this is autoimmune-related (e.g., an anti virus-neural cell component).

- Diagnosis is by clinical presentation plus temporal association, usually in week 2 post-vaccination. Classic CNS disorder symptoms include sudden onset of headache and vomiting in week 2 post-vaccination. Convulsions and lethargy progress to coma, paralysis, focal neurologic signs in any combination. Cerebral edema is evident with massive increased intracranial pressure. Compatible CSF findings
- Treatment: Supportive care only.

Miscellaneous other complications such as hemolytic anemia, arthritis, osteoarthritis, pericarditis and myocarditis have been seen.

Adverse events and treatment with VIG. A chart was presented (Lane *et al*, JID, 1970; 122:303-309; Pediatrics 1969; 39:916-923) of the expected number of adverse events from vaccination with vaccinia (smallpox) vaccine, presented in rates per million doses. The estimated populations with contraindications to smallpox vaccination included:
Recipients of solid organ transplantation: 184,000 (progressive vaccinia)
Cancer patients and survivors: 8.5 million
HIV infected: 900,000 (Known diagnosis: 550,000; Unknown diagnosis: 300,000)
Atopic dermatitis: 28 million
Patients on steroids, chemotherapy, etc.: Unknown

Prevention of adverse effects from vaccination includes: adequate screening to avoid vaccination in those susceptible persons, and in susceptible contacts of vaccinees: pregnant women, immunodeficient or -suppressed persons, those with eczema or atopic dermatitis), disruptive skin disease, conjunctival and corneal disease. There are questions about the use of VIG in some of those susceptible individuals who are contacts; this would be decided on a case-by-case basis. Use of antiviral therapy may be warranted for them. VIG will be used in those inadvertently vaccinated, and antiviral therapy may be used. The studies provide some experience in the use of attenuated vaccine as well.

Committee discussion included:
- *Is the vaccine virus spread by contact?* 20% of VIG requests were for treatment of contacts, mostly close contacts, much less so for respiratory contact. No known studies reflect a household contact developing antibody without a lesion. If 10-20% of VIG requests are for management of contacts, presumably at least that number of serious reactions may be represented by contacts as opposed to primary vaccinees.
- *What is the degree of contagiousness in the prodrome?* Data suggest that stage is not infectious for most cases. Infectiousness begins as the smallpox patient develops an ananthem, which breaks down and releases virus through oropharyngeal secretions. The Sakar study of viral titers in throat swabs found the highest titers beginning about day 3, the beginning of the macular stage/rash, when virus tends to persist more in higher-titer individuals with more severe illness. But unless an attack is known, smallpox is unlikely to be considered as a differential diagnosis of those in the macular/papular stage. The noninfectiousness of the pre-rash period was indicated in mouthwash studies by Downey and in Madras. They found no virus preceding rash, but fairly extensive virus after onset

of rash.

- *What data show protection by VIG given simultaneously and that it will not abort the vaccine response?* There is no hard evidence that it does work. The data are empiric, based on observation of those children who had serum antibody but no CMI, who developed progressive vaccinia at the primary vaccination site, but no viremic lesions. The hypothesis then was that without viremia, viremic spread cannot occur. But there is no way to know what would have happened without giving the VIG, because a number of patients were immunized without complications.
- *Are second generation cases in the household more severe, as seen with varicella?* Unknown.
- *Are there any data on risk factors in the immunocompomised for hemorrhagic or flat smallpox?* Pregnancy is a risk factor, as is an immunocompromised state, and age may be.
- *What data are there on increased vaccinia risk among pregnant women?* Dr. Gall reported several studies in 1949 after the 1947 New York City epidemic. The ~2750 pregnant women who were immunized with smallpox vaccine in their first trimester showed no difference in adverse reactions or teratogenic rate versus the ~1375 who were not immunized. If the immunity is cell mediated, more adverse outcomes could be expected in the second or third trimester, as seen with paralytic polio. Dr. Schwartz reported data on pregnant women in the 1963 Stockholm outbreak. Of 170 vaccinated pregnant women in all trimesters no serious complications were seen among the mothers. But two of three early spontaneous abortions may have been vaccine-related; as may have 5 stillbirths and 3 neonatal deaths. That was a 4.75% rate of stillbirth/neonatal death versus the 2.65% rate of neonatal death the prior year. The rate of premature births paralleled that of the general population, and no infants had any evidence of fetal vaccinia.
- *What is "weaponized smallpox"?* Dr. Henderson reported it possible to dry smallpox, as done with anthrax, with stabilizers added to let it persist in the air as an aerosol for a long time. The U.S. program did this before it was ended in 1972 and the Vergosov article last November reported successful studies of an aerosolized smallpox on an island in Aral Sea. But little is known of Soviet Union studies.

Production/Deployment/Risk Benefit of Smallpox Vaccine

Production/Supply of Smallpox Vaccine and VIG

Dr. James LeDuc, of NCID, outlined the contents of the national smallpox stockpile: Wyeth Dryvax® (1:1– 15 million doses and 1:5 dilution – 75 million doses), Acambis vaccinia vaccine in MRC5 cells (Acam1000 – 54 million doses contracted to be produced), Acambis vaccinia vaccine in vero cells (Acam2000 – 155 million doses to be produced for a one-time purchase); and the Aventis Pasteur (AvP) vaccine (~86 million doses produced in the mid-1950s). In September 2000, CDC contracted with Acambis to deliver a new vaccine. This 20-year term of this contract is unique, to avoid supply interruptions and to serve as the backbone of the national smallpox vaccine supply. Only the AvP and Dryvax® vaccines are available today.

Rehydration of the Dryvax® vaccine by .25 ml of vaccine increases the total to 100 doses, and a

1:5 dilution produces 500 doses. All orders include delivery of individually-wrapped bifurcated needles: 15 million for the original Dryvax® stock and 60 million for a 1:5 Dryvax® dilution. Along with an additional 75 million ordered, this will supply a needle for every dose in the National Pharmaceutical Stockpile (NPS). The contract provides for a diluent for 1:5 Dryvax,® to be provided under an IND at least to the end of 2003. A contract is now being negotiated for VIG supplies (30,000 doses and an option to increase if needed).

Dryvax® is the source for the plaque purified new Acam1000 and Acam2000 vaccines. The Acam1000 and Acam2000 vaccines share a master seed that makes the products very similar. The Acam2000 product has been grown in bulk and Phase II trials are underway; 150 million doses of vaccine should be ready by October 2002. The Phase I clinical trials for Acam1000 are almost completed; Phase II trials are scheduled for this summer. Production of the Acam1000 will continue into the next calendar year. With these and current stocks, a dose for every citizen is anticipated by the end of this year. There have been no "surprises" in the clinical trials to date.

In summary, vaccine will be in hand for all Americans by the end of 2002; all vaccines are now under an IND status; clinical trials through Phase II should be completed by the end of 2002; licensure of cell-culture vaccines should be accomplished in late 2003 or 2004; and the production contract includes the delivery of bifurcated needles and vaccine diluent. A contract calling for 30,000 doses of VIG is under negotiation now, but that may not be fulfilled until January of 2004.

NPS Vaccine Storage/Deployment

Dr. Lisa Rotz, of NCID, reported that the initial vaccine could be delivered by deployed CDC smallpox response team(s) within hours of notification to site(s) with suspected case(s) or a high-suspicion rash. Vaccination would begin as soon as smallpox is confirmed. Additional vaccine can arrive within 12 hours of activation.

The NPS storage sites have been identified to allow rapid deployment. Product can be delivered to all 3556 cities in the U.S. with >10,000 population within 5-7 days. The NPS is working with states to identify where the vaccine would be delivered.

Target distribution goals. The first 75 million doses of smallpox vaccine are packaged on "Vaxicooled" systems for rapid deployment. These are self-contained shipping/storage units able to maintain the cold chain for both shipment and storage on site. Each Vaxicool can hold 300 vials (150,000 doses per Vaxicool system, diluted 1:5). The target goal is to have 500 Vaxicools ready to ship throughout the U.S. within 24-36 hours, where the vaccine will be stored at multiple locations. Ancillary supplies to arrive with the Vaxicools include the diluent, transfer needles for vaccine reconstitution and bifurcated needles for single use administration.

Shipments of the remainder of the NPS vaccine will be sent in styrofoam shipping containers that require on site storage. These containers can accommodate 10,000, 15,000, or 150,000 doses/container, and will require local planning and equipment for vaccine refrigeration and storage. The NPS capability goal is to deploy all 280 million doses of vaccine within five days to

multiple locations throughout the U.S.

The IND protocols address:

1. Non-emergency use (pre-event): a local responsible principal investigator is onsite; full written informed consent is obtained; adverse event monitoring and reporting is in place. The vaccine's use is only for persons aged ≥18 years.
2. Emergency use: CDC is working with FDA and DHHS to develop a streamlined informed consent process to vaccinate large numbers of persons in all age groups.

Discussion included:

- *What is the soonest the vaccine will be available; some states want to have a cache of vaccine in each state.* The latter will be negotiated over time; currently the NPS is ensuring that they can respond to the need quickly. The Acambis 2000 vaccine should be in vial form in the next month or two, certainly by October, but how much cannot be definitively stated yet. For the near term, the vaccines in hand are the Dryvax® and the AvP products.
- *Do the new or existing doses have a dye marker in the diluent?* No dye is currently in the diluent used under IND to reconstitute Dryvax.®
- *What studies are planned for children on the new tissue-derived smallpox vaccine?* Dr. Heilman reported a protocol developed to look at that the use of Dryvax® in children. But these studies are still in discussion, as are Acambis' plans for the pediatric populations. Mr. Tom Monath of Acambis said that it is still at question whether pediatric studies should be done or if adverse effect reporting should be used. The studies may be necessary, but no plans to do them are developed. Acambis will respond to what the scientific and medical community thinks should be done. Dr. Abramson reported unanimous COID opinion on two occasions that these studies need to be done. Children cannot be left to be their own experiment in an emergency situation. He was very disappointed that these are not further along.
- *Which vaccine product would by used by the state response teams, if ACIP recommends they be vaccinated, and would that depend on VIG availability?* The states will wait for the Acambis vaccine for use in a pre-attack scenario, but current requests (e.g., for lab workers at risk from working with orthopox virus) are being met with the Dryvax® vaccine. Discussion will be needed if it further coverage requires wider vaccine use.
- *What is the VIG dose?* The 30,000 treatments contracted are based on a 70 kg person, at 0.6 ml. The new VIG will be an IV formulation as opposed to the old IM formulation.
- *Are there any engineering controls to ensure the bifurcated needle is not redipped?* No, not other than their being individually wrapped, which makes them unlikely to be reused. The sharps disposal method will be the same as for hypodermic needles.

Smallpox Risks/Benefits of Pre-Exposure Vaccination

Dr. Martin Meltzer, of the NCID Office of Surveillance, discussed the balancing of smallpox risks versus the probability of the risks of vaccine side effects. Smallpox risks include the probability of release, the number of persons initially infected, probability of contact, rate of transmission, and vaccine effectiveness.

His model's decision rules are such that, if the risk balance is ≥0, an individual should logically accept pre-exposure vaccination, since the risk of smallpox is greater than that of the vaccine-related side effects. But if the risk balance is <0, an individual should not logically accept pre-exposure prophylaxis, since the vaccine-related side effects exceed the risks of smallpox disease. Only the "serious" vaccine-related side effects are considered; those that would require significant medical intervention, such as the use of VIG and likely more than one visit to a physician for follow-up. The model did not include, in the estimation of the risk of serious side effects, the risk of transmission to family members and/or those at high risk. Including those factors would alter the risk-benefit equation and make it even less likely that a pre-exposure vaccination should be accepted (i.e., more likely that the risk balance would be < 0).

The assumptions used in the model are that: 1) the individual evaluating the risk and benefits of vaccination is risk neutral (i.e., all other items being equal, all potential vaccine users will equally value a case of smallpox to a case of serious, vaccine-related side effects); 2) the results of the model only apply to the pre-release scenario. Risks will be re-evaluated after discovery of a release; and, 3) the model takes the perspective of the individual.

Risk estimates. The results shown were calculated using the following assumptions regarding a release:

a. Number of persons infected before the release is known: 1,000.
b. Probability of a smallpox release: range from 1:100 to 1:100,000.
c. Probability of contact with an infectious person or being infected in the initial release: range from 1:100 to 1:10,000.
d. Probability of transmission from an infectious person to a susceptible person: 0.70.
e. Vaccine effectiveness: 98%.
f. Rate of serious side effects due to vaccination: 1:100,000.

Hospital Personnel: For hospital employees to logically demand and accept pre-exposure vaccination, they would have to simultaneously assess the risk of release at1:1,000 and the risk of contact at 1:100. The risk of contact of 1:100 is equivalent to assuming that 100,000 healthcare workers are at risk and 1,000 cases would occur before detection. To assess the risk of contact before discovery of the outbreak, one must consider the facts that the U.S. has ~5,100 hospitals (1997 data), which annually host 96 million visits to their Emergency Departments, and employ 88,800 physicians and dentists, 800,000 full-time and 400,000 part-time nurses, and 2.79 million other salaried employees. For the mid-Atlantic region alone, there are 446 general hospitals, with 12.5 million ED visits/year, employing 18,000 full-time physicians and dentists, 158,000 nurses and licensed practical nurses, 24,000 trainees and 430,000 other salaried staff (e.g., clerks, laundry workers, janitors). Considering those numbers, the actual probability of hospital personnel coming into contact with smallpox is far below 1:100. Thus, using the results from the model, a hospital employee would not demand pre-release vaccination.

General Population. Even at a 1:10 potential probability of release, it would not be logical for a member of the general population in the U.S. to demand pre-event vaccination because the risk

of side effects would be greater than those of smallpox. This result is true even if only 9 million persons, representing a metro area, are at risk of being involved in the initial release, before detection.

Investigation Teams. If it is assumed that the risk of release is 1:100,000 and the risk of contact is 1:5, a member of an investigation team would, using the model results, demand and accept pre-exposure vaccination. This calculation was made assuming that the risk of transmission would be reduced to 40%, due to the fact that the response team is unlikely to approach a risk situation without protective equipment. If the risk increases above 40%, the advantage of pre-exposure vaccination increases as well.

Sensitivity analyses: general population. In the initial set of results, one case of smallpox was equated to one case of vaccine-related serious side effects. Some people, however, may place a far greater value on avoiding a case of smallpox than avoiding a case of serious, vaccine-related side effects. There could be several reasons for this, including the fact that for persons who have no contra-indications for smallpox vaccine, the risk of death from vaccination is approximately 1-in-1 million persons vaccinated. But, up to 30% of those who contract a case of smallpox may die from the disease. However, even if an individual equates one case of smallpox to 30 cases of serious vaccine-related side effects, a member of the general population would not, using the results from the model, demand pre-exposure vaccination. This result is true even if the risk of release was as high as 1:10. Dr. Meltzer himself would decline pre-event vaccination.

Thus, if a member of the general population were to demand and accept pre-exposure vaccination today, without knowledge of an outbreak of smallpox, we know that the person making such a demand is valuing one case of smallpox to 30 cases of serious, vaccine-related side effects. However, such valuations regarding vaccine related side effects may dramatically change when the general population is confronted with the actual reality fo smallpox vaccine related side effects. The U.S. has a history of valuing the avoidance of vaccine-related side effects, as seen with OPV and whole-cell pertussis. As the public becomes more knowledgeable of the vaccine's serious side effects, the number wanting pre-exposure vaccination may decline.

The most important variables in determining these risk-benefit ratios were:

a. Risk of release. Any ACIP statement will implicitly or explicitly make a statement about the risk of release.
b. Risk of contact before discovery -- important, but a low probability among 280 million people.
c. Risk of vaccine-related side effects, especially with immunodeficient or other immunologically naive populations. Good screening must be considered essential.

The summary conclusions were that:

a. Pre-exposure of hospital personnel is not justified since the risk of side effects exceeds the risk of disease, unless risk of release is 1:50.
b. A member of the general population would not accept pre-exposure smallpox vaccination

unless the risk of release is 1:10.

c. Vaccination of a small number of investigation teams may be justified where the risk of contact is assumed to be 20% (1:5).

Discussion included:

- *Is the likelihood of an adverse effect larger than those of Dr. Lane's studies of 30-40 years ago?* The results presented were calculated assuming a 1:100,000 risk of serious side effects. The larger the risk of side effects, the less acceptable is the receipt of vaccine. There is no guarantee that the risk would go down to zero, even with extensive screening.
- *Please clarify the 1:10 risk of release; surely that does not that mean that one in ten of the U.S. population would be exposed? And what was the relative risk during the mass vaccination period (e.g., in the mid-1960s when smallpox importation was likely), using this model? Would it support vaccination?* The 1:10 risk of release is a 10% risk of attack with smallpox in the U.S. This is a time-dependent function relative to the period of the vaccine's protection (which is unknown). The model would still apply to the scenario involving the risk associated with importation of cases of the 1960s.

Occupational Health and Safety Issues in Smallpox Response

Dr. Scott Dietchman, of NIOSH, discussed the occupational health and safety issues related to smallpox response. The Bureau of Labor Statistics indicates that hospitals employ 5.1 million persons; all health services employ almost 11.5 million individuals. There are 4000 EDs, 32,000 ED physicians, 89,000 ED nurses, 815,000 EMS providers, and 17,000 ambulance services. The BLS and the National Fire Prevention Association estimate a total of ~2.3 million responders in these categories in the U.S.

The transmission lessons of the smallpox experience indicate a risk to close contacts and the possibility that infectious aerosols can travel long distances. For that reason, *standard precautions* and contact and airborne precautions are involved in smallpox infection control. "Standard precautions" include hand washing, wearing non-sterile gloves, gowns, and the use of masks/eye protection or face shields. *Contact precautions* also involve wearing clean gloves upon entering the patient's room, wearing gowns for all contact with the patient and his environment, removing the gown when leaving the room, and washing hands with an antimicrobial agent. *Airborne precautions* add still more: respiratory protection (N95 or better), housing the patient in a negative air pressure room with 6-12 air exchanges/hour, keeping the patient's door closed, and discharging the air outside or through HEPA filter.

Beyond vaccination, exposure is prevented through an occupational health hierarchy of controls:

1 Administrative controls: work practices that limit the number of workers potentially exposed and those that limit exposure to the hazard.

- Engineering controls: Isolation rooms under negative pressure that are tested daily. A check by the New York City health department in 1998 found 38% of airflow in "negative pressure" rooms blowing *outwards* and automatic airflow monitors that were wrong 50% of the time (e.g., their fan were installed backwards during routine

maintenance). The negative pressure can be simply tested with a smoke tube.

- Personal Protective Equipment (PPE) and respiratory protection for smallpox: Particles <5 microns can be suspended in air, dispersed by air currents and deposited in the lungs. NIOSH recommends fitted respirators that meet or surpass the NIOSH N95 standard (e.g., N100s have a better facial seal and fit). To be compliant with OSHA regulations, a program must have training, maintenance and fit testings, as already recommended by CDC in 1994 for TB prevention. Data support that fit testing is essential. Leakage measured at 33%-95% declined with fit testing to only 4% leakage in 95% of respirators. There also are more protective respirators such as Powered Air-Purifying Respirators (PAPR) and hood respirators. These provide 25-fold more protection, or 50 times more with a tight-fitting mask. The disadvantages of these include cost, equipment weight, battery dependence, and noise that can interfere with patient care. The PPE chosen depends on the risk.

Discussion included a question of how many public health workers in the U.S. would be estimated as doing the vaccination and case identification? No one knew; Dr. Dietchman suggested checking with ASTHO or NACCHO.

Public/Provider KAB Research: Smallpox-Related Knowledge and Beliefs: Disease, Vaccine and Immunization Strategies

CDC Communication Research Findings. Dr. Glen Nowak, of the NIP, reported on their April 2002 survey of public and provider smallpox-related knowledge and beliefs. The research purpose was to determine perceptions and misperceptions, in order to assess the communication efforts that will be needed. The 10-day study, done in Philadelphia, Chicago and San Francisco, included 17 one-on-one in-depth physician interviews and 20 public focus groups (8/group), which included separate and mixed ethnicities in ten groups each of females and males.

Physician knowledge and beliefs about smallpox reflected the following:

1. Overall, limited knowledge about smallpox disease. Misperceptions include that infectious disease specialists and pediatricians were most familiar with vaccines and immunization, but most had smallpox training >20 years ago or knew of it only by historical reference. Some thought that smallpox still occurs naturally in the developing world and there were questions about disease transmission.
2. There was little knowledge about smallpox vaccine and its administration, the latter particularly among younger physicians (aged ≤35 years).
3. Vaccine was assumed to be effective because smallpox was eliminated and to be as safe as the routinely recommended childhood vaccines, since it was recommended.
4. It was assumed that CDC could/would effectively screen for contraindications and severe vaccine adverse events.

Policy beliefs, pre-attack. Beliefs about the current ACIP recommendations, pre-attack, reflected understanding of the existing policy and general support for limited pre-attack use of smallpox vaccine. Those with higher perceptions of personal threat (e.g., living on the east coast

and ED physicians) were more in favor of expanding pre-attack recommendations to include "first responders" and/or some physicians, and more were personally willing to be vaccinated pre-attack.

Strategies beliefs, post-attack. Physician beliefs about current ACIP recommendations (post-attack) included little knowledge of "ring" vaccination, especially among younger physicians aged <40 years. Ring vaccination was counter-intuitive for many who were trained that mass vaccination provides maximum protection. They recognized that ring vaccination would be needed and helpful, but no one believed it could be the sole strategy in the event of an outbreak. Most supported supplementing ring vaccination with rapid and broader access to vaccine (e.g., permissive vaccination as for a meningitis outbreaks).

Concerns expressed about ring vaccination cited much that has changed since the 1960s, including:

1. Lower levels of population immunity that in the past may have enabled the success of the ring vaccination; greater numbers of immune-compromised individuals and a more mobile society; and that the disease will be artificially introduced, most likely with numerous and unknown index cases. These concerns led to worry about an inability to identify all the people who will have been potentially exposed.
2. The anthrax experiences engendered skepticism about any potentially "dated" strategy (e.g., are current medical/public health assumptions valid, and is confidence warranted that old approaches will work today, especially regarding a bioterrorism attack?)
3. The public will demand vaccine and trying to limit access to it will be impractical. Give it to all who ask for it, if the vaccine supply is sufficient.
4. Mass or broad vaccination was considered more attractive and feasible than any large-scale quarantine of people.

Other key findings learned from the physician survey included:

1. Great concern about liability issues, especially in pre-attack public vaccination.
2. Opinions of little support for pre-attack permissive vaccination were based on personal beliefs and social concerns rather than science. Rapid access to smallpox vaccine was preferred. Some thought ring vaccination to be an unfocused or random approach, not a public health strategy to disease control/containment, particularly relative to an outbreak.
3. The threats of smallpox and bioterrorism are remote to physicians compared to the immediate demands of daily practice, although this would change quickly if an attack occurred.

Public smallpox knowledge and beliefs were:

1. Overall, there was little knowledge about smallpox disease. Many had misperceptions, and there was much uncertainty about symptoms. Many believed that exposure nearly always results in death, that the disease can be transmitted by casual contact, and that smallpox occurs naturally in the developing world.

2. Most cited CDC as the best source of information about a disease like smallpox.
3. There was little knowledge about smallpox vaccine and its administration.
4. Many assumed that the vaccine is safe and provided lifetime protection.
5. Older participants thought that children still receive smallpox vaccine as part of the routine childhood schedule.
6. Most wanted to receive vaccine if an outbreak occurs in the U.S. or in their state.

Pre-attack. Public beliefs regarding the smallpox vaccine's benefits and risks:

1. The desire to receive the vaccine was most strongly related to threat perception.
2. Most thought the frequency of adverse events was small and unlikely to happen to them. Fact sheets and pictures of vaccine adverse events had little impact on their desire for vaccine. If interested, they still wanted it, but those not interested in vaccine expressed reluctance even in the event of an outbreak.

Public beliefs regarding vaccine use were:

1. The existing policy was understood and accepted. The public generally supported very limited, pre-attack use of smallpox vaccine.
2. Pre-event permissive vaccination had some appeal (e.g., it provided freedom of choice).
3. Those who recognized the public health perspective favored mass ("required") vaccination in the event of an outbreak. Nearly everyone favored broad access in the event of an outbreak.

Public beliefs regarding ring vaccination were:

1. When explained, most still had a hard time understanding the approach.
2. "Selective" vaccination raised concerns about equity and social justice (e.g., race, culture, SES), and most felt that ring vaccination would be insufficient to stem an outbreak.
3. Vaccination was equated to broad or mass vaccination, as done with other vaccines.
4. The participants wanted to know how health authorities could/would know who had been exposed .
5. Again, the anthrax experiences engendered skepticism about this strategy.

Harvard Public Opinion Survey

From May 8-21, 2002, Harvard University conducted a public opinion survey if 3,011 adults. The margin of error was ~2%. The survey was third in a series on "Americans' Response to Biologic Terrorism;'" the first two were done in October and November-December 2001.

When asked if they would be vaccinated as a precaution to a terrorist smallpox attack, 59% of respondents said yes; 33% said no. Fifty-six percent thought they had been vaccinated for smallpox; 8% thought they were likely to contract smallpox (versus 70% who thought influenza likely); 43% were "worried" that terrorist might use smallpox in attacks (8% very worried and 35% somewhat worried). Forty percent believed there is a cure for smallpox and 84% were "confident" (45% "very" confident) that their physician would recognize the symptoms.

Comments Received by CDC Website
Of 789 total responses to a CDC Website poll over a 12-day period, 65% of the respondents were female and 35% were male. About 21% were in health care or hospital occupations, 14% in public health, 4% in emergency response or law enforcement, and 60% were in the general public.

The answers were coded according to the three questions and options of focus to this ACIP meeting:

- Question 1: The majority agreed with Option 1 (status quo, not vaccinating the public at large); Option 4 was next in preference (vaccine available to those who want it – 1 and 4 were somewhat equivalent), followed by Option 3, and by Option 2 last (again, three and two were somewhat equivalent).
- Question 2 (vaccination of response teams/early responders): Options 1 and 3 were somewhat equivalent; Option 2 was the least desirable.
- Question 3 (ring vaccination as a primary strategy): Option 1 was supported, but Options 2,3,4 received more support than the current option, to provide broader access to vaccine upon an attack.

In summary:

- Smallpox disease and vaccine knowledge is quite limited. One challenge is that public/practitioner attention may be decreasing.
- There were strong preferences were illustrated for ACIP to make a clear recommendation on vaccine use versus a neutral recommendation.
- Expansion of pre-event vaccine use will necessitate much provider and potential vaccinee education; one challenge will be to effectively provide vaccine benefit/risk information.
- Significant expansion of pre-event use of vaccine likely will be interpreted by many, including healthcare providers, to signify an increasing smallpox disease threat.
- Much support was voiced for post-event vaccine use strategies that supplement "ring" vaccination with rapid, broad access to vaccine.

Discussion included that there is a difference in perceived threat risk nationally, declining from east to west.

Public Policy Options

The Case for Voluntary Smallpox Vaccination
Dr. Don Millar drew the Committee's attention to a case succinctly described by the by Bicknell article (*NEJM*), which was in the meeting books. Dr. Millar was ACIP's Executive Secretary (1978-1981), and is a physician/epidemiologist with 41 years experience in infectious disease, epidemiology, and later in occupational and environmental health. From 1963-1970, he directed CDC's smallpox elimination program. Based on that experience and his resulting bias, he wished to offer one point.
On one occasion during his work in the Indian province of Behar, the first outbreak response

team was ineffective; smallpox re-emerged and was re-contained with surveillance and containment measures. In following up, he met a boy aged ~8 years who had been blinded by smallpox. The first door-to-door containment team did not find and vaccinate him, and the second team arrived after the vaccine could prevent it. His likely future as a beggar in the rural India of 1975 was worsened by indolent public health workers.

Whether vaccine should be made available to the U.S. population hinges in whether or not the threat of a smallpox attack is real. On a scale of hypothetical to certainty, what is the probability? The government's budget requests infers a real threat, but its withholding of vaccination (the only effective primary prevention) from the public until after an attack infers that the threat of attack is imaginary.

Experts cannot accurately estimate the threat without all the information. The threat cannot be meaningfully estimated based on tales of Soviet defectors and media accounts. But, Dr. Millar believed, someone in the Executive Branch does know, and the public is entitled to an accurate probabilistic estimate of an attack. Without that, no one can meaningfully participate in developing a vaccination policy or rationally follow whatever policy is established.

ACIP is the principal advisory group for immunization policy, and as such has a potentially powerful voice. Dr. Millar advised the Committee to demand that the administration "put up or shut up" about smallpox bioterrorism. If there is no threat, the government should stop behaving as if there is and demanding enormous expenditures only justified by a real threat. But if the threat is real and significant, a good reason is due to the public for withholding the vaccine.

His conclusion, based on his knowledge of smallpox and vaccination, was to accept on faith that a bioterrorist smallpox attack is not only feasible but likely (i.e., >50/50). Those exposed to smallpox have much greater risks than those of vaccination; he termed the latter "insignificant" in comparison. So to him, the current national policy to withhold vaccine from the public makes no sense. The policy to withhold it should either be convincingly defended, something not done to date, or the vaccine should be made available now to those who want it.

Widespread Smallpox Vaccination; Effects on Blood Donor Deferral

Dr. Dorothy Scott, of FDA's Center for Center for Biologics Evaluation and Research (CBER) reviewed the issues of vaccinia immune globulin (VIG), including the supply, potency, and licensing of the current VIG and VIGIV products, as well as the anti-vaccinia antibody activity in the licensed IGIV products. She agreed that the supply of VIG is the limiting factor in the scheduling of vaccination. She also clarified that the VIG dose is calculated at 0.6 mg/kg of weight for a 70-kg person. However, practically speaking, several variable may change this. For example, the historical conventional treatment for EV was 1-5 mg/kg, so the dose may be higher. The supply also depends on the weight of those requiring the VIG.

Background. The standard deferrals for blood donation by the American Association of Blood Banks (AABB) for those who have received attenuated viral and bacterial vaccine are two weeks (for measles, mumps, polio, typhoid, and yellow fever) and four weeks (for rubella and chicken

pox). The default deferral for other vaccines is 12 months.

In the U.S., ~13.2 million units of blood are collected annually from only ~5% of eligible donors. On average, there are 8.25 million donors, who typically repeat their donations. Previous donor deferrals have affected the donor base: 1) hep B core antibody testing resulted in a loss of up to 3% of donors; the change of the cutoff level of a donor's hemoglobin by the American Red Cross (ARC), which collects ~50% of the U.S. blood supply, cost 5% of their donors; and just since June 2002, the new regulations for travelers to countries with BSE have lowered donations 5-10%.

The emphasis on monitoring the blood supply has enabled much better determination of supply status. FDA's conclusions (and actions) are that mass smallpox vaccination could affect the blood supply. But the amount can be minimized since the deferral depends on the recommended deferral time. Since post-vaccination viremia is believed to be transient and uncommon in normal vaccine recipients, it is unlikely that viremia could last six months after vaccination. That means that the default position for "other vaccines" could be altered. In response, with CDC and the blood community, the FDA Working Group on Blood Donor Deferrals is developing specific interim recommendations on blood donor deferrals after smallpox vaccination, to ensure blood supply and safety. They also plan to refine any interim recommendations based upon ongoing FDA and industry studies to detect viremia post-vaccination using modern methods.

In *discussion*, Dr. Birkhead commented that the BSE deferral has uneven impacts across the country. For example, New York could lose up to 35% of their blood supply from donor deferrals after mass vaccination.

Smallpox-related Meeting/Poll Reports

IOM Meeting

Dr. Charles Carpenter reported on the well-attended June 15 Institute of Medicine meeting on smallpox, for which no formal report will be generated. Presentations were provided on the clinical/epidemiologic features of smallpox; the information that can be gained from models; important vaccine issues such duration of immunity; and on the considerations learned by the Washington D.C. public health officials from the anthrax situation. Opinions on policy options were provided by first responders and medical personnel, and ethical and communication issues were discussed.

The meeting achieved a strong consensus on several points:

- There should be a clear national recommendation on the use of smallpox vaccination.
- The recommendation must be delivered by carefully chosen, trusted national spokespersons who should deliver a consistent message.
- The message must be straightforward for the public to understand it.
- The policy adopted should be neither too directive nor too permissive.

Responses to the three questions under examination were as follows:

- Question 1: general concurrence to continue the current recommendation to not vaccinate the general public before attack, without modification.
- Question 2: There was no consensus whether individuals in specific occupational groups, in addition to the current lab personnel covered, should be vaccinated to enhance preparedness. Some felt vaccination should be available to individuals predesignated by appropriate authorities to respond. Some also felt that vaccination should be extended to additional "essential" predesignated medical and non-medical personnel. There was no consensus, but it was strongly felt, that if vaccination is recommended for those categories, it should be strictly voluntary and provided with informed consent.
- Question 3: There was agreement to retain ring containment as the primary strategy, but many felt it should be supplemented with vaccination of medical, health, law and other personnel who would assist in response, taken voluntarily and only with informed consent. There was little or no support to vaccinate all individuals who do not fall in the ring vaccination area.

In other issues, it was repeatedly emphasized that panic will be a problem. It is necessary to proactively educate the general public to minimize panic based on unrealistic fears in the unlikely event an outbreak occurs.

ASTHO Poll

Dr. Edward Thompson, of the Mississippi health department, reported on the first survey conducted by Association of State and Territorial Health Officers (ASTHO) of its members on public health policy issues. He clarified that this was not an official ASTHO policy statement, but reflects the opinion of the members. A June 4 conference call was held for public health officials to outline the information presented at this meeting. Then, on June 4-5 on the ASTHO Website, the opinion of the states' chief health official (or their designee) was solicited on DHHS' three questions about smallpox vaccine use. Forty-three states responded and one territory, an 86% response rate.

Question 1: 91% favored Option 1, to effect no change to the current statement, in a pre-event scenario. Option 2 was favored by 7%; Options 3 and 4 drew no votes. Concerns expressed were:

- A recommendation against pre-event public vaccination with a "permissive" caveat would place state/local health departments in the undesirable position of providing a vaccine that is not recommended
- A permissive policy would create a situation of inequity across the general population, as implementation would inevitably differ from state to state.
- A permissive recommendation without significant limitations about who should receive the vaccine would result in significant vaccine wastage, due to the large dosage size of the vials, and could compromise the ability to respond if a large scale event occurred subsequently.

Question 2: Regarding pre-event vaccination of designated potential responders in the state bioterrorism plan. 7% percent favored Option 1, 77% favored Option 2, to pre-vaccinate state

volunteer response teams of 6-9 individuals; and 16% favored Option 3 (to add a few more essential designated healthcare personnel). In the aggregate, 93% favored pre-event vaccination of some individual responders likely to be exposed.

Question 3: Post-event ring vaccination as a primary strategy supplemented by other strategies was supported, but "primary" must be clearly defined a only the first choice of several that will be augmented according to circumstances, not as the sole response strategy, a common misunderstanding.

In summary, the ASTHO polls reflected these opinions:

- State health departments would like a small cache of vaccine stored in each state for immediate vaccination (i.e., within hours of an outbreak) of additional responders.
- State health departments emphasized the need for a comprehensive campaign to educate the public, providers, and elected officials about smallpox disease and risks/benefits of the vaccine.
- State health departments strongly emphasized the need for rapid vaccine deployment capacity and the assurance of that capacity to the public and providers.
- While state health departments do not view broad-scale vaccination of groups or mass (voluntary) vaccination of the public as a primary response to the appearance of specific cases, there is an underlying understanding that the capacity to conduct large scale or even mass vaccination must be assured.

Discussion reported similar discussions by the Council of State and Territorial Epidemiologists (CSTE). It was also noted that the "first responders" to a biological attack will be different from those traditional responders to any other kind of attack. For that reason, specification of who those individuals should be should be left to the states, using CDC/ACIP guidelines.

Community Forum Summaries

Reports were provided by Drs. Birkhead and Smith on two of the three community forums held around the country to discuss these questions and options.

New York. Dr. Birkhead reported the forum held in New York City at Mt Sinai hospital. It involved 150 participants from 14 organizations (state nurse and medical societies, Columbia School;, of Public Health, hospitals, etc.), and the general public. The responses were:

Question 1: There was no real support for a general population vaccination recommendation, although some supported availability to those who want vaccination in consultation with their physician.

Question 2: There was wider support for vaccination of health care workers, and some for ED workers, ambulance and EMS workers. During 9/11, people did not go to designated hospitals, but to the nearest one. The hospitals were again flooded by people demanding antibiotics during the anthrax attacks. For those reasons, there was support for providing vaccine to ED workers and public health investigative teams.

Question 3: There was support for the surveillance/containment strategy, but the New York City health department spoke of potential widespread transmission (e.g., through the subway system) that might require a vehicle for some widespread vaccination.

Other issues requiring attention were the need for a clear communication plan, engagement of the media to get the message out; education and training for medical groups and for essential staff; for the public; and for those who would participate in a mass vaccination campaign. There was support for a state cache to ensure that vaccine is immediately available. Widespread pre-vaccination probably would incur a lot of vaccine wastage. A clear policy is needed about health care worker deferral after vaccination, to avoid shutting down the health care system. Finally, the expansion of VIG supplies was seen as critical. In public comment, several individuals expressed concerns that ring vaccination would be inadequate(e.g., with widespread transmission in the subways), as well as concern that personal rights are violated by quarantine and mandatory vaccination.

San Francisco. Dr. Smith attended the meeting in San Francisco, California. The responses were:
Question 1: Agreement to not vaccinate in a pre-event scenario.
Question 2: Agreement that state/local governments need some capability to respond quickly, and to the need for vaccinated state/local response teams. There was less of a push to vaccinate health care workers, but at least some physicians should be ready in pre-designated facilities.
Question 3: Surveillance and containment was endorsed at the primary strategy. In an outbreak, equitable vaccination in communities that are less accessible or educated must be assured. Circumstances might warrant extended vaccination. Finally, the importance of state and local infrastructure and planning, and of education, was stressed.

Discussion included:

- Dr. Henderson reiterated that transmission on subways and airplanes is unlikely, since infectiousness only rises with the prodrome and rash, periods of great illnesses. The prodrome is not infectious until the rash emerges, so transmission is likely to be limited to household or hospital contacts. He also noted the problem with state caches due to FDA expiration deadlines. These can be retitered if properly stored, but if stored in every state, much of the vaccine will be lost. Finally, he raised the logistical problems to be solved: a) the vaccine comes in 100-dose vials, and once reconstituted, deteriorates more rapidly than in the dry state. Trials are needed to see how long the vaccine is viable after reconstitution (apparently ~10-14 days), and then has to be discarded. No smaller amount than the current 0.25 ml of suspension can be bottled in equal amounts. And b) as an IND, the vaccine requires IRB approval for distribution, with a responsible person in change who reports on follow-up. Whatever is done, if more vaccine is given, all these require consideration.
- Dr. Midthun commented that the 18-month expiration was set due to the inability to ensure Dryvax'® potency once it leaves the manufacturer. The expiration of vaccines in development, such as the Acam1000 product, will be determined with their development.

- Such details as the 1:5 dilution possible for Dryvax® need to be made clear to the public. The logistical issues of vaccine delivery and follow-up will require ACIP's attention in the next few months.

Public comments of up to 5 minutes were solicited, to good response. The names of those who signed up to speak were randomly drawn.

Dr. Stanley Plotkin agreed with the working group's conservative recommendations, which should be accompanied, as done in recent ACIP statements, by research recommendations. He hoped for more information about smallpox delivered by the aerosol route. An outbreak in the former Soviet Union was apparently aerosol-produced, and some question whether smallpox delivered by that route is more virulent than that delivered by contact. It is possible that the strains used may not be traditional variola major and that the aerosol route would produce a different type of smallpox in a different distribution of clinical syndromes than that of contact transmission. An aerosolized smallpox dose also may be analogous to the surprising infectivity of anthrax in individuals who inhaled only a few spores. While it is comforting that vaccinia vaccine apparently controlled the Soviet Union epidemic, more information is needed. The latest science on canarypox as a possible vector indicates that canarypox viruses can be engineered by insertion of cytokines that results in a different biological behavior. Vaccinia virus also contains immune response modifying (dampening) genes, which could feasibly be used to decrease the immune response of individuals.

While it is probably unlikely that any individual terrorist is sophisticated enough to do these things, nation states are. Consultation is needed with Russian scientists now working on protection against smallpox, and those working in the past to develop smallpox. An open exchange of information is needed between these two countries, which now are discussing universal vaccination. He reminded the Committee that vaccinia is not an attenuated smallpox, but a natural virus depending on cross-reacting and neutralizing t-cell epitopes. It is easy to imagine insertion of epitopes that are not reactive to vaccinia.

Finally, a better vaccinia is needed against smallpox, not just safer mutants like MVA or Niovac, but also viruses that are more immunogenic and provide better protection. This can be done in the current realm of microbiology, but it must be a research objective.

Dr. Deborah Wexler, Executive Director of the Immunization Action Coalition, expressed the coalition's formal support of the ACIP working group's recommendations on smallpox.

Mr. William Tell, of the Advisory Board Company of Washington, D.C., a research and consulting firm for the hospital industry, spoke as a private citizen and parent. He urged the ACIP to allow the American people the option of smallpox vaccination. He based this on the event of 3000 Americans killed on 9/11; the knowledge that smallpox can be weaponized and that hostile nations such as North Korea and Iraq have smallpox research; on the fact that our enemies have demonstrated a willingness to die; and on the evidence suggesting that public health could not respond adequately to widespread attacks. A smallpox panic could force a

lock-down of many of the nation's hospitals, which are already on ED diversion much of the time, potentially causing the deaths of many trauma, heart attack, etc., victims. Children may be infected and kept out of school until their fever goes down, but the parent may not see the rash developing in their child's mouth. The American people paid for this vaccine with their taxes and should have the right to choose vaccination with the advice of their physicians. He expected an extraordinary backlash if the ACIP denies access to this vaccine and an attack occurs. He felt that the defense against smallpox is herd immunity, and he and his family "want to join the herd." In fact, he reported that his wife does not want to become pregnant again until she is vaccinated against smallpox.

Ms. Kathi Williams, director and co-founder of the National Vaccine Information Center (NVIC), stated their opposition to vaccination prior to an attack. Her son incurred minimal brain damage from a routine DPaT vaccination. Thanks to the hard work done to make vaccine safer, most Americans equate "vaccine" with "safe and effective." Few comprehend the potential spread of the disease to vaccinees' contacts and the terrible potential outcomes. Some consider it a patriotic duty to be vaccinated. She urged the ACIP to stand behind the ring vaccination strategy. There is no reason to subject citizens to the vaccine's real and significant risks; no "all or nothing" policy is needed. This vaccine caused greater adverse effects than any vaccine every used, and, since vaccinia is no longer circulating, selective introduction is almost impossible. World-wide vaccination will be required, causing immeasurable suffering to tens of thousands. Finally, Ms. Williams read a statement from Col. Redman Handy, resigned from the Air Force Reserves due to his objections to anthrax vaccination. He cited the cost to the American taxpayer of pilots who resigned due to mandatory anthrax vaccinations, and he recommended, before advising vaccination of first responders, asking the question of how many the U.S. can afford to lose due to unnecessary reactions to premature vaccinations.

Dr. Sherri Tenpenny of Cincinnati, Ohio, also a member of the NVIC, noted that the slow spread of smallpox, only after intense close contact, implies that few cases will occur. The scenario of millions of deaths is a fear-based assumption, not a factual conclusion. CDC's and the Defense Advanced Research Program Agency (DARPA) lists of agents of biological and biochemical warfare are long, and smallpox is only one. Many other diseases are even more deadly; what if they are introduced after everyone is vaccinated for smallpox? She quoted the much higher vaccinia-related mortality rates reported in the morning's presentations. Many of the complications that were fatal in the last smallpox cases in the U.S. can now be treated. If honest informed consent is provided, it must be clear that the risk of the vaccine exceeds its benefits. She supported the use of the surveillance and containment strategy, and urged the Committee to not recommend the release of an IND and this virus into the general public.

Kris Ehresmann, of the Minnesota health department, asked the ACIP to consider the impact of the adverse effects of a smallpox vaccination program on future smallpox immunization programs, on routine immunization programs, and on future mass vaccination that would be needed, such as for the pandemic influenza that is considered to be inevitable.

Dr. Jonathan Goldsmith, Medical Director of the Immune Deficiency Foundation (IDF) of

Baltimore, MD, expressed the IDF's concerns about the approaches to vaccination. Individuals with inherited primary immune deficiency are a fragile population that could suffer morbidity and mortality with an expanded vaccinia program. Fifty thousand such individuals were identified in the IDF's 1996 and 2001 surveys, and even more have not been identified. They risk complications from the immunization and from contact with those immunized.

The IDF recommended:

- A stockpile of IGIV sufficient vaccinia antibody titers for the currently licensed product. About 70% of their patient population now uses IGIV. A stockpile should also be created for the general public.
- A hyperimmune globulin (VIG) should be produced, stockpiled and distributed for prophylactic use in such fragile populations as those with primary immune diseases, as strategies for vaccination and ring containment advance.
- A potential screening algorithm for smallpox vaccinees could include: have you had an organ or bone marrow transplant?; do you/family member have chronic problems with skin or skin conditions like eczema?; are you or a household member pregnant?; and last, do you or any family member a) have trouble with frequent infections requiring treatment with antibiotics, or b) been told about a problem with your immune system? No to all four questions invites vaccination; a yes or uncertainty invites further screening. Additional questions could be whether the person has been hospitalized to treat infections, and how many times? ($\geq$2, do not vaccinate); were they were diagnosed with an immune system disease, or if a family member was so diagnosed (If yes, do not vaccinate); if they take antibiotics three or more times a year (if yes, do not vaccinate and refer to their physician for evaluation).

If vaccination programs are initiated, the IDF's strategic recommendations were:

- Make VIG available for prophylactic use; FDA should license an IV preparation.
- If a vaccination strategy is undertaken, VIG should be made available to those with Severe Combined Immune Deficiency Syndrome, Wiskott-Aldrich Syndrome, Common Variable Immune Deficiency DiGeorge anomaly, Ataxia Telangoectasia, and other T-cell defects.

Mr. Bill Phillips expressed his appreciation of the input and openness at this meeting. This was not seen in the related legislative process in Georgia, which disregarded issues of medical ethics, informed consent, considerations related to pregnancy and immunodeficiency. Citizens asking about informed consent were accused of being anti-patriotic. None of the 25 people at the legislature to speak to the issues were allowed to speak until after the vote was taken. In short, public input was suppressed, despite the support of the state health director. The smallpox issue was politicized by the government's drive to pass legislation to show it was addressing the problem. Some provisions essentially would force involuntary vaccination, violation of the Nuremburg code and medical ethics. He urged the Committee to allow vaccination for those who want it, but not to force it, and to push for funding for the required related education of the public.

Dr. Alan Hinman was director of immunization projects for 30 years, was the Executive Secretary of the ACIP and NVAC and is now again an NVAC member, but he spoke as an individual. He found the smallpox vaccine to be a very good one, but as with all vaccines, it has risks and benefits, and its risks are greater than other vaccines now generally used. No vaccine is currently licensed for use, so it must be administered be under IND authority, which involves many administrative processes. The predictable rate of adverse effects could affect future immunizations, and there is a shortage of VIG. There is no proven risk of smallpox exposure, and without that, there is no reason for a change.

He advised the Committee to choose Option 1 for Question 1 (no change in the current recommendation); and Option 2 for Question 2 (expanding vaccination to medical care personnel, each state having one or more vaccinated teams identified to work alongside CDC teams [<10,000 individuals nationwide]). But Question 3 is more difficult. The primary strategy to interrupt transmission should be search and containment, but recognizing that it might be hard to rapidly identify all those contacted, and due to public concern, it might be wise to do mass vaccinations in defined geographic areas, but not nationwide – a mix of options 2,3,4. Finally, once the vaccine is licensed, he advised making it available to all who request it, but that does not mean that ACIP should recommend it for everyone.

Mr. Joseph DiPisa is an independent biomedical engineer who has examined vaccine delivery issues for the last few months. He raised several logistical vaccination issues that the ACIP will need to stay engaged in beyond the questions posed. In the event of a massive attack, which he believes to be possible, critical logistic issues will include the training needed to allow public health staff to safely and effectively deliver the vaccine. The mathematical modelers will have to stay engaged to help the switch from a search and containment ring vaccination strategy to one of a mass vaccination strategy. He also noted that, while public strategies are important in addressing such big issues and help to engage the nation, this also is a national defense issue. Some plans need to be private, those needed to deploy the defense mechanisms necessary to save people's lives in the event of a massive outbreak.

Dr. Arthur Yancy, of the National Association of EMS Physicians, asked the Committee to consider, for pre-exposure immunization of occupations at high risk, development of a schedule of the likely time periods of known side effects. This will allow these services, (EMS, ED, etc,) to immunize their personnel in a tiered manner to ensure the uninterrupted continuation of vital services.

Mr. Steve Allred, a nurse practitioner, asked if the side effects and complications of the 1:5 dilutions are more, less, or the same as the 1:1 vaccine. Dr. Heilman reported equivalent common reactions between the 1:5 and 1:10 dilutions, although there were some variations. Dr. Snider recalled the interesting and counterintuitive increase of satellite lesions in the 1:5 dilution versus the undiluted vaccine. Dr. Margolis reported less induration, less erythema, etc., as would be expected. But these were also tested in highly screened populations, so while the severe adverse effects would not be expected to be seen, local and systemic adverse effects were seen.

Dr. Eric France, of the AAHP, drew the participants' attention to a letter from the President of the AAHP, which posed a number of question for the ACIP's consideration. Issues of vaccine delivery are always a challenge, one the ACIP has recently taken up to address (e.g., considering the delivery of influenza vaccine to 6-24 month-olds). He urged the Committee to consider, also as pertains to smallpox, the issues of who will give the vaccine, who will pay for those who are uninsured or not covered, who will pay for adverse effects, etc.

Dr. D.A. Henderson provided some additional information on the Russian outbreaks. Russian press reports of Russian scientists suggested that wide-scale vaccinations may begin this autumn for the 18 months thereafter. Despite numerous such reports, this was officially denied. There was a report at the IOM meeting on the 1971 outbreak by Dr. Zandlinskas of the Sandia National Laboratory. A 93-page document translated by the Defense Intelligence Agency provided a compendium of Russian reports on that outbreak. It documents ten cases, three of which were hemorrhagic, and seven were among individuals previously vaccinated. Last November, a report was issued from the former Soviet Union Vice Minister, Pieter Brogosov, tracing the outbreak to studies done on an island in the Aral Sea where they did most of their outdoor testing of biologic weapons.

The first case appeared in a woman (but not the 12 crew members) on a small boat doing studies on the sea. The boat never came closer than 15 km to the island. But the Vice Minister reported that they were working with aerosolized smallpox at that time, which presumably is how she became infected. The reporter assumed this must have been an especially virulent strain. Of the ten ensuing cases, three occurred in children, who died; and another was reported in a 20-year old woman. To have three of ten cases be hemorrhagic is unusual, but not impossible. Five of the seven who recovered were vaccinated previously as children and were over 30 years of age, and one vaccination does not protect for a lifetime. It is possible that the aerosolization caused the infection.

But what is not explained is the three generations of cases: the first case infected on the boat, the next three cases, and the balance of six in the third generation. The problem is that a major epidemic in northern Afghanistan was exporting many cases to areas of Iran near to the Afghani provinces. One of these was a clear outbreak of aerosolized smallpox. Another outbreak in Germany was traced to a coughing smallpox patient on the ground floor, who infected 17 people (some on floors 2 and 3) as well as a person looking for directions who opened a door 30 feet away from the patient. This was clearly an importation into Germany, with aerosol spread involving very few particles. The evidence is that aerosol spread is possible; smallpox has been prepared in a dry stable form, as was anthrax. But how likely it would be used to spread smallpox is unknown.

Dr. Sam Katz drew attention to a letter distributed from Dr. David Gilbert of IDSA, which agreed with what Dr. Thompson had presented for ASTHO. IDSA asked if the same people on the state/municipal teams would be responsible for initiating a vaccination program in that area, or if another team would do so. He also noted that Cidofovir® may be used as an antiviral, and is

now used to treat HIV. But is only available for IV administration, not orally, and it is highly nephrotoxic. However, he also had read abstracts of less toxic materials demonstrating greater effectiveness when used in mouse models and he asked if more information was available on this. Dr. Levin referred him to the slides on antiviral treatment presented at the Smallpox Working Group which may answer that. Dr. Midthun mentioned that there are provisions to use Cidofovir® under IND in the event of certain complications.

- *In the German outbreak, what was virulence of the secondary cases?* Dr. Henderson reported 3-4 deaths in all. The hemorrhagic cases did not lead to more hemorrhagic cases, nor did the malignant or flat cases followed in Madras regenerate. The feeling is that this relates more to the individual response than the strain itself.
- *What was the actual cause of death of smallpox?* The actual cause is still mysterious; it could be some sort of cytokine storm or release of general toxemia, etc. Most of the pathology examined is from older work, but little of that was done during the global program. But for hemorrhagic cases, some form of coagulopathy is involved, as evidenced by extensive bleeding into the skin and intestinal tract that leads to rapid death after onset. On the other hand, most of the mortality of ordinary smallpox cases occurs in the second rather than first week of illness. Dr. Orenstein also referred the group to the Havens data from the Smallpox Working Group, which speculates death due to a severe inflammatory response. If that is true, the anticipated mortality rate should be much better if the current standards of care can be provided to all those infected.
- Dr. Mack added that many people who die have, in effect, of third degree burns over a substantial portion of their bodies. He speculated that there may have been electrolyte and renal problems involved in some cases. He in turn asked if smallpox immune globulin had ever been collected from people with smallpox scars. Dr. Henderson responded that the Madras study by Fulginiti of vaccinia IG (not variola), tested the serum of 300 patients of smallpox, who had 20-100 times the level of the IG. This suggested that variola IG would be a better product than vaccinia IG. However, they were producing IG from patients who recovered from variola, which was not very successful as a therapeutic agent. He agreed to provide the reference later.

Report of Literature Review

Dr. Benjamin Schwartz, of the NIP, reported on the NIP's review of the literature to explore, relative to vaccinia vaccination: the rates of mild, moderate, severe, and more serious adverse events; the potential impact of screening for high risk conditions on the rate of serious (VIG requiring) events; and the degree to which VIG requiring events may occur under pre-event vaccination and screening scenarios. The review included published data from 1963 and 1968 by CDC and NIH in vaccinating response teams and dilutional study subjects, respectively; and Swedish outbreak data. They estimated VIG needs for the current U.S. population and developed screening strategies to identify high-risk persons for whom pre-event vaccination should be deferred and to estimate the impact of screening.

CDC analysis

Moderate adverse events were defined as those requiring a medical care visit (outpatient) or time

lost from work or school. The results for a *robust primary reaction* were 4-18%. It may be confused with cellulitis, depending on the education of the health care provider (risk per vaccinee was 1:25 to 1:5.5).

The results, per one million primary vaccinees and one million revaccinees, respectively, were as follow:

- *Generalized vaccinia,* 250 and 42 (more common among infants; less common among those <20 years old; VIG occasionally used for therapy (risk per vaccinee 1:4,167 to 1:100,000).
- Inadvertent inoculation, 529 and 42 (severity depends on site; VIG occasionally used for therapy; risk per vaccinee 1:1,890 and 1:23,809);
- *Erythema multiforme*, 165 and 10, respectively (risk per vaccinee 1:6,060 to 1:100,000).
- *Other events* in the NIH dilutional study involve 12 of the 665 study population (1.8%) visiting an ED or hospitalized (risk per vaccinee 1:222). Of those, two were related to vaccination, 7 were unrelated, two probably were not, and one possibly was. Two were related. Up to 36.4% were "sufficiently ill to miss school, work recreational activities, or to have trouble sleeping."

Serious adverse effects of vaccinia (smallpox) vaccination were defined as death, encephalitis, and events requiring VIG therapy. The data sources were from 1963 and 1968 national surveillance and CDC projections with and without vaccinee screening considered. The types of events calculated for one million primary vaccinees and revaccinees, respectively, and the risk per vaccinee, were:

- *Death.* Risk per vaccinee of 0.8 to 1.1 for primary vaccinees, 0.0 to 0.2 of revaccinees; (risk per vaccinee of one:one million to 1:5 million). Of 16 deaths, 2 (12.5%) occurred in contacts of vaccinees, only one death in a person >20 years old. Causes of death were encephalitis (9), vaccinia necrosum (4), and eczema vaccinatum (3).
- *Encephalitis:* 1.9-2.9 primary vaccinees, none for revaccinees (risk per vaccinee of 1:400,000). (State surveillance, however, reported 3.4 to 12.3 and two cases, respectively.)
- *VIG requiring events:* 1968 surveillance data: 74.7 and 4.7, respectively (risk per vaccinee of 1:13,387 and 1:212,766). CDC estimates, for the current U.S. population without screening, are 214:1 million (risk per vaccinee of 1:4,677); estimate with screening: 3.4 to 54.5 per million, depending on the intensity of screening (risk per vaccinee of 1:294,118 to 1:18,349).

The caveats associated with this analysis are:

- There are no data on risks of serious adverse effects associated with revaccination after 30 or more years.
- Data are very limited on rates of adverse effects in the elderly.
- CDC estimates for serious events requiring VIG therapy are based on several assumptions and limited data.
- Estimates for the effectiveness of screening in deferring vaccination for those with contraindications should be evaluated further.

- The estimated impact of screening may be less if serious adverse events occur in persons with no known risk factors (i.e., among those who do not have an immunocompromising conditions or history of atopic dermatitis).
- These estimates do not consider risk among pregnant women who may be vaccinated.

Stockholm 1963 Outbreak Analysis.
In response to an outbreak in 1963, Swedish authorities vaccinated ~350,000 persons with a locally produced vaccine. Of these, ~19% were "epidemiologically indicated and the remainder was "mass vaccination; up to 60% were revaccinations. Adverse events were reported to and hospitalized at the infectious disease hospital. Of outpatient visit rates of 1:400, the adverse events were: lymphangitis (26%), erysipelas rash (24%), postvaccinal rash (21%), secondary pox (15%), and daughter lesions (14%). Inpatient rates were 1:1,800) for: encephalopathy (7.3%); pericarditis/myocarditis (2.7%); eczema vaccinatum (3.7%); generalized vaccinia (3.2%); vaccinia necrosum (1%); and lesions as seen in outpatients (82%).

Adverse events related to vaccination of high-risk persons were also reported for 131 persons at risk from steroid or radiation therapy, chronic disease including diabetes mellitus and malignancy, a history of encephalitis, and age >60 years. Of these, 7.6% had severe local reactions, 7.6% had generalized reactions, and 10 received VIG. (See previous reported data on the 170 pregnant women vaccinated in all trimesters).

Discussion included:
- This is a good vaccine; it eliminated this horrific disease. However, Dr. Lane expressed concern that presenting a horrific picture of the adverse effects will frighten the public. The medical system will be overwhelmed If only 1-2% of vaccinees seek medical care. People need to be prepared that fever, rashes, etc., are a normal part of the vaccination. The VIS for vaccinia should clearly define the robust primary reactions and erythematous rashes not as adverse effects, but as normal expected outcomes of primary vaccinia inoculation. The Stockholm data of 1:400 outpatient visits after vaccination are illuminating in this regard.
- *What about post-vaccinial encephalitis, permanent or serious neurological resulting sequelae?* Dr. Lane reported that ~25% die and ~25% have mild to serious sequelae, about what would be expected with infection encephalitis.

Mathematical modeling of sequelae and expected benefits of pre-event vaccination.
Dr. Schwartz described John Glasser's mathematical model to evaluate the impact of pre-event vaccination on the subsequent course of a potential outbreak. The model was applied to any individual defined as to their susceptibility or immunity (residual from infection or previous vaccination). After the disease is transferred to the respiratory tract, during the early incubation period, vaccination can still abort the infection. Later in the incubation period, the spectrum of disease may still be modified by vaccination and limit dissemination. Still later, the disease outcome will not be altered, but isolation is a key component of public health response. The majority likely to survive will be immune to infection.

The Glasser model analyzed the transitions between these states using differential equations. This model was presented to the Smallpox Working Group, a smallpox modeling forum at NIH, and others. It uses discrete math to address public health questions. When validated by applying the Bangladesh and Stockholm outbreaks, it reflected actual data well.

Scenario: smallpox attack in city of 3.5 million people, no control measures implemented; disease introduced by ten cases; 40% of the population with some residual community and 60% are entirely susceptible. Several different hypothesized R^0's were used: 3, 5, and 7. The data on the R^o of 5 were presented. With an R^0 of 7, basically the entire population would become infected.

A response of search and containment was applied, assuming the effectiveness of identifying and isolated cases (90% identified, 95% of those isolated) and their contacts (75% identified, 75% of those isolated), and assuming appropriate timing of vaccination and isolation. If ten cases are introduced to the same metro area, with an R^5, nine incident cases would occur in week 2-3, rapidly declining until<1 case/week would be identified in week 29. Mass vaccination of 50% of the U.S. population would prevent 1-2 cases/week.

Modeling data suggest that if not only close contacts but also a second ring of individuals are vaccinated in the community of the case, the same decrease of cases could be achieved as would be achieved by wide-scale mass vaccination. If 10,000 people are vaccinated for every infected case, the same rapid decrease in disease as through pre-event wide-spread vaccination. Dr. Schwartz offered to incorporate other model scenarios for the ACIP, as desired, to be considered before the Committee's decision.

Committee discussion included:

- *One problem is the lack of information on massive aerosolization, since these discussions and most of this modeling is based on the assumption that the transmission route will be by infected people entering the U.S.* Dr. Meltzer's model presentation was based on of 10 carriers, but simultaneously introductions by 100 people were done, and 1000 or more could be done.
- *One over-estimation of these models is their use of the same R^0 for succeeding generations, and a population that is independent in succeeding generations. That is not the case; the social framework is shared often by the first and second generations, and so the R^0's will be different.* Dr. Glasser responded that the R^0 is a benchmark of a wholly susceptible population, and it changes with succeeding generations.
- *To make these decisions, the ACIP needs data. Those on vaccine efficacy and safety are in hand, but not for the risk of disease. Does anyone have more information on this that they can share? Without it, should the ACIP even make this decision without that information?* Dr. Modlin stated, according to the best information published, presented at meetings, and discussed by Dr. Henderson and others, that ACIP was unlikely to have better estimates of risk than it now had. A higher-level briefing arranged for Committee members may be possible, but he thought that such would be unlikely to alter any decision reached on this day. Dr. Snider agreed. Some information inappropriate to

share in a public forum could be provided, but the bottom line would be the same as the message being received here today. The CDC Director would not place on this Committee the burden of making a risk assessment. The members were informed as best as possible under the circumstances that the risk is not zero but is perceived to be low. Any change in that status will be conveyed to the Committee. If the risk is determined by others to not be low, it is hoped that the government policy would change, since the ACIP's assumption of low risk was not correct.

- The current estimate was charted that, with no pre-event vaccination to 50% pre-event vaccination, the number of cases that would occur by week. Less than one incident case with 50% vaccination would occur at about 7 weeks; with no pre-event vaccination, that would occur at about 20 weeks. Between those two curves, the number of cases prevented by vaccinating as many as ~140 million people could be estimated.
- *Have calculations been done that assume the identification and vaccination of half the exposed contacts now assumed?* The 90% of cases identified/10% not identified, and 75% of contacts identified and isolated are felt to be reasonable assumptions. But if only half are identified/vaccinated, the same type of modeling produces a higher curve, and it would take longer to achieve <1 case/week. Those results could be presented to the Committee. Dr. Peter urged that this be done. If ACIP decides not to recommend permissive vaccination, much weight is placed on surveillance and containment. In investing the resources for that, not only curves but numbers will be very important to have.
- *What was the success of contact tracing/isolation in the smallpox elimination program?* Dr. Lane responded that nothing less than 100% was acceptable; the program would go back again and again until that was achieved. He could not conceive of a situation in the U.S., with 50 patients identified with smallpox, that their contacts would not be identified. Rather, if anything, he expected that "contact" might be over-defined and more than necessary would be identified.

Presentation by the Council of Economic Advisers

Mr. Douglas Holtz-Eakin, Chief Economist of the Council of Economic Advisers (CSA), described their modeling and economic analysis of a smallpox attack, as related to the epidemiology and the economy. He began with three take-away points:

1. The economic costs of a smallpox attack are an order of magnitude or larger than the public health costs often discussed.
2. Therefore, consideration of the economic costs should enter into any decision. Bringing those economic consequences into any analysis of the risk of an attack shifts the critical probability downward in deciding the point at which a vaccination policy makes sense.
3. In thinking about policies in advance of such an eventuality, one option is to inoculate not just the population against an attack, but the economy as well, through "economic first responders." This would keep the economy functioning in the aftermath of an attack, as well as address the public health problems.

Economic analysis of a smallpox attack. The economic costs of a smallpox attack would be large. For example, a shut-down of the transportation system would affect the vital artery of the

economy. In considering immunization strategies, the economic costs in the CEA analysis dwarf other costs. The implication of their benefit-cost analysis, avoiding non-economic costs, suggests a strong consideration of broader pre-attack vaccination.

The costs of disruptions in economic activities include:

- Full lock-down: Everyone stays at home, no one works or travels: the GDP would drop 90% at a cost of $177 billion/week. Fallout from 9/11 was larger because of the shaken national confidence and pervasive impacts on the economic outlook for the population, causing national effects from a local event.
- A major disruption in inter-city travel. Travel is contained to prevent disease transmission by policy or individual choice. People can go to work, but few cross the border of any metropolitan area. This would close ~80% of the transportation system, at a minimum cost of $41 billion/week. Grocery shelves would surely be quickly emptied in an outbreak and could not be restocked.

Four vaccination strategies to contain such an attack were considered, modeling the epidemiology (mortality/morbidity) and economic impact of a transportation shutdown (an estimated loss of $180 billion/week):

1. No pre-attack vaccination, vaccination after attack done as fast as possible.
2. Pre-attack vaccination of public health first responders, as well as economic first responders (pilots, truckers, etc.) to keep the economy functioning.
3. Mass voluntary pre-attack vaccination.
4. Focus on public health first responders as a pre-attack vaccination strategy.

The benefit/cost analysis, including economic costs, supports consideration of a general pre-attack vaccination policy. If the probability of attack is very low, the best strategy is no vaccination; as it rises even modestly, pre-attack vaccination for first responders (both public health and economic) is wise. Pre-attack voluntary vaccination on a mass scale becomes more logical as high risk approaches. The public health first responders' vaccination is never the dominant strategy; the economic costs must be also be considered.

The analysis conclusions were:

- Some form of widespread pre-attack vaccination merits strong consideration. The probabilities at which it becomes the dominant strategy are modest.
- "Economic first responders" play an important role in minimizing the economic costs of a smallpox attack.
- Consideration of the economic costs of smallpox attack generally support more widespread pre-attack vaccination strategy, and dominate the narrower public health costs.
- The optimal vaccination strategy depends on the risk of attack and the economic as well as health consequences of the attack.

Committee discussion included:

- *Please elaborate more on the number of those discussed as "economic first responders",*

aside from transportation workers. This is needed to consider vaccine supplies and the logistics of vaccinating that many people. This is not a discrete category, but rather an ascending scale. Truckers, pilots, and railway engineers are followed by a minimum set of warehousing/distribution employees from central to local sites, then to retail outlets. The numbers range from large to as small as specified.

- *Assuming that since none of the transportation workers are likely to be exposed, is the assumption that they will not come to work rather than that they would be contacts or at high risk?* There are two components to the formal analysis: the epidemiologic model that, in the event of an attack, 30% of those contracting the disease die while others are sick and out of work. The other cases consider that in a metro area, people may be ordered or the individual may elect to go home. The effect of these latter cannot be teased apart in a formal analysis. Dr. Snider commented on the inability to know the strategy of sophisticated adversaries. Any subsets of the population could be targets.
- *But then there is almost no end to it; this could involve half of the U.S. population, if taken to an absurd point.* Dr. Dietchman reported his collection of data on the number of transportation workers: 3 million truck operators would rise to ~10 million if dispatchers, mechanics, all warehouse workers are included. There are fewer rail workers (~250,000-300,000) and fewer still air transport workers.
- *The CEA model assumes the need to vaccinate these people pre-event, but an alternative is to quickly do so post-event, decreasing the economic disruption according to the best model scenario. What were your assumptions?* The CEA analysis is not stressing so much the particulars of the numbers as the need to include the economic costs, which will always shift the result toward mass vaccination. Done with Office of Homeland Security, this analysis assumed a large introduction, with ring vaccination effectively ending mortality after ~45 days, and then adding in the economic disruption from a full lock-down of metropolitan "bubbles" of no work (losses of economic activity, etc.), while unaffected metro areas would continue, minimizing the economic disruption. The scenarios are phased to a complete resolution within 45 days.
- *What percent of population was assumed to accept vaccination?* An estimated 76% of population was analyzed as accepting pre-attack vaccination. Polling data indicate 50%; if advised the day of an impending attack, it could be 100%.
- *The smallpox eradication strategies never considered a total economic shutdown. What scenario is driving this analysis?* An aerosol exposure in an airport, with resulting unknown dissemination.
- *The problem with this scenario is that the disease has already been spread widely, so shutting down transportation doesn't make sense. And 2) in anthrax, the fear factor was there. Did you examine the impact of intangibles like fear on going to work, etc.?* The CEA looked at the anthrax effects, but those were mitigated to a great extent by people's willingness to go to mail substitutes such as e-mail, fax, etc.
- Dr. Meltzer took from this analysis the message that panic must be controlled. The English outbreak in Birmingham demonstrated this, in which a shutdown was avoided due to information released to the public. But there was a shutdown in Cardiff, in the absence of such information. That factor could greatly alter the outcome of the analysis.
- *What would be the cost impact of economic disruption with a fully vaccinated population*

and a smallpox introduction? A mass voluntarily vaccinated population would have unvaccinated persons, involving loss of life, morbidity, etc. That was included in the analysis, which anticipated ~400-500 deaths, valued in economic terms. Pre-event vaccination is presumed to reduce panic tremendously, and the analysis reflects that as well.

Committee Discussion of DHHS Questions

After a short break, Dr. Modlin invited discussion of the questions posed in the Committee's charge. A working group was to begin writing a proposed supplement to the smallpox statement on the coming evening, to help the Committee's discussion on the next day. Points offered included the following:

- Remove question 3, and instead incorporate the ring strategy and related possibilities into the assumptions. Presumably, surveillance will be done anyway; assume that ring vaccination and containment will be a successful strategy and include it as a prelude to the two questions that are the real issues.
- Note the success of the ring vaccination strategy which was discussed as part of an outbreak response that also includes offering broader vaccination.
- Specifically craft preamble language to address preparation, education, the necessity of flexibility, and recognition that some change will be necessary to the statement should the assessment of the threat change. Clearly state in the preamble/assumptions that the Committee was informed that the government's judgement is that the risk of an attack is low, and that other simultaneous activities to ring containment will occur as needed.
- Define ring containment, ensure its clarity in the smallpox response plan, and provide great detail on it when the ACIP statement is revised.
- *Why do the Wyeth and Aventis vaccines remain under IND status and what is the plan to appropriately license them*? They both are likely to remain IND products. Studies could be done to change that, but the likelihood of the Acambis products' licensure at some point, makes the worth of investing in that is questionable. There have been discussions with the company to do the testing to relicense Dryvax,® but the 1958 Aventis vaccine was produced under standards different than today's. The preference is to keep that in reserve and to use the more sophisticated strain production of the Acambis product. NIH is moving in parallel tracks with multiple products to see what could be licensed quickly.
- *The Dryvax® liability problem, related to its need for a diluent, is not an ACIP issue, but should that be considered?* Dr. Snider said no. Indemnification issues are important and are not insurmountable, but as with any other vaccine, they should not constrain ACIP's consideration of who should be vaccinated. The Committee should recommend based on the information provided, and let DHHS deal with those problems.
- *How is "community" defined in Option 3?* This is an important question with no easy answer. It will vary between states and communities. The concept is of a group of people with sufficient social/geographic cohesiveness to have some probability to be in the first ring of contacts. In the U.S., this might not be geographical; it could be any place providing a high rate of contact with the first cases, such as at a reunion or a mall.

There is time to define that group and to reach them through media outreach when needed. Dr. Orenstein termed that as a decision that will have to be made "on the ground," considering the extent of the attack and the outbreak, public demand, vaccine supply, etc. What needs to be clear is the need to have the capacity to vaccinate the entire population in a given area of any size, within a short period. He recommended that the discussion focus on pre-event vaccination.

- State health officials have made clear that the state response plans, which describe what is done in ring vaccination (a term that should be changed to "search and containment") to contain the first two rings, must also be clear that this is not all that is done. That has not been adequately explained, and is needed. In fact, it should be placed in the preamble.
- Critical issues requiring attention after this meeting include: logistics/methods to do screening; in the context of an event, how to use a vaccine; screening in a clinic setting, involving (potentially multiple) IND IRBs; ACIP and other agencies' participation to implement and monitor in an ongoing fashion any extended vaccination program from the current model; and education of the public on the ring containment strategy.

Dr. Modlin checked the Committee's evolving opinion on the three questions asked.

QUESTION 1: Lack of preference for any option other than Option 1 indicated a consensus to favor Option 1.

QUESTION 2: The consensus of the working group had been to begin focusing on Option 2, but the text is perhaps not yet clearly defined. It could be modified. Dr. Modlin asked for comments on Option 2 or Option 3.

- The states want a consistent policy across states, balanced with some flexibility (e.g., to predesignate sites).
- Option 2 is preferable, but CDC/ACIP need to continue examining this issue for the lessons learned, to consider whether any changes are warranted over time. As discussed and agreed earlier, ACIP will continue to monitor the situation and the program, how the safety data emerges, the status of threat and whether the recommendations should change. Stated clearly in the preamble that ACIP will monitor the entire environment associated with smallpox issues (e.g., vaccine risks, capacity, etc.).
- If Option 2 is chosen, the functionality of that, rather than details, should be the focus.
- A query to the Surgeon General may be warranted to seek a decision about vaccinating the Commissioned Corps, who are not covered under the current recommendations and plans.

With no further comment, the meeting adjourned at 6:32 p.m.

JUNE 20, 2002

Upon reconvening on the following morning, Dr. Modlin made several announcements:

- Dr. Roger Bernier's project to enhance public involvement and broad partnerships in the

vaccine policy-making process will hold a first consultation conference on July 31-August 2 in Racine, WI. Dr. Modlin asked for a volunteer to represent the ACIP at that meeting.

- An ACIP working group on human papillomavirus (HPV) vaccines, now in Phase III trials, and on HIV vaccines, will be formed before the October meeting. Members interested in participating were asked to notify Dr. Modlin.

Review of the Draft ACIP Supplemental Statement on Smallpox Vaccine

Dr. Joel Kuritsky reviewed the draft supplement to the smallpox statement written by the working group overnight. It included a preamble, introduction, a definition of ring vaccination, the assumptions behind the policy, and the recommendations themselves. The draft document that resulted from the following discussion is posted on the CDC Website http://www.cdc.gov/nip/.

Discussion included:

- The text on "local" public health officials is open to various interpretations. It was suggested to leave that at "state," which will have its own designated teams. However, much response happens at the local level, and greater detail such as where facilities would be sited is part of the local plan.
- Move Question 3 into the Introduction's text.
- Move surveillance/containment into the preamble and reference those as "including ring vaccination as a component of that strategy".
- Insert the ACIP's periodic review of these recommendations, new information, etc., into the assumptions as well. A compromise was agreed to keep it in the front of the document but to bold it as well so that it stands out.
- Include "the experience gained in the implementation of these recommendations" to what would be reviewed in an ongoing fashion by an oversight group. Be clear that the latter will be formed.
- Change "Assumptions" to "Critical Considerations," and expand the text of the second bullet to address the level of disease and threat, specifying that the ACIP is proceeding based on information "presented to ACIP."
- Add to the section on "smallpox vaccines and availability" a sentence to indicate the assumption that VIG will be available in increased supply beginning in 2003.
- There is a lack of data on vaccine use among children. Insert a strong statement of this as an important research need at least for efficacy data, if not for safety data. While the data are in hand for Dryvax,® that is not the case for the Acambis product, which is cell-cultured and may be more or less immunogenic. Its use in a clinical setting without supporting data cannot be advised, making this is an FDA decision.
    - As the testimony of the previous day indicated, there are parents who want their children immunized and would likely be willing to participate in the trials. However, in the absence of a proven risk, asking parents to assume another unknown risk from the vaccine essentially requires them to evaluate the risks themselves. While this is true in all studies, this is not an ordinary study. Counseling would be required and more than normal caution would have to be

exercised, to say the least.

- It was reiterated that the implicit assumption in hand is that a smallpox attack would use the familiar smallpox that is not disseminated by widespread aerosol. There is a danger in using the tactics of the last war to fight the current one. However, the document's intent is not to specify the mode of exposure, but to address the transmission after exposure, which will occur through the regular mechanisms.
- The NIH/NIAID Vaccine and Treatment Evaluation Units assessed the feasibility of conducting a study of the 1:5 Dryvax® in children, NIAID. Consultation with experts led to the conclusion that a well controlled, well-designed study is needed. Children likely to be involved will be those not in daycare, without siblings and staying at home with a parent. This has been reviewed by DHHS and by local IRBs in the past months. It is hoped that some form of the study will go through, which will also provide some framework for Acambis and future vaccine studies. The more complete statement to be reviewed in October should also state the need for pediatric studies and other research on the Acambis vaccine as well.
- Testing in children is important, particularly since the Acambis product probably will be widely used when released. The younger children who are excluded from studies could also be studied. The NIH has discussed extending the Acambis products' use beyond the 2-5 year-old group. The question is how to do it, and how pressing the need is.

- Add to the section on pre-release that the older vaccines are reserved for emergency use and, barring that, any vaccination will await release of the Acambis product. Make it clear that taking the vaccine will be totally voluntary.
- *State teams: one or more per hospital?* The workgroup's intent was to tie the teams to predesignated hospitals as defined in the interim smallpox plan, and to have sites independent of hospitals from which patients would be referred to physicians for care. This is framed as a suggestion or guidance to avoid being too prescriptive. Variables affecting this include geography, where hospitals are located, etc.
- If the ACIP expressed a vaccine preference, that would help the implementation group develop their time lines. However, in this early vaccine development stage, with limited data, no vaccine preference is yet possible. While the ACIP could do this if asked, several members expressed reluctance to state a preference for an unlicensed vaccine. That was only done once, for anthrax vaccine last fall, and only on relatively circumscribed issues. The list of future issues needing address could include investigating a vaccine preference. Re-evaluation will be needed even if the situation remains static. This could be bolded in the introduction and reinforced at the end, and perhaps also list the likely issues to be addressed.
- Also helpful would be the ACIP's acknowledgment that the implementation of these recommendations will take time and will require resolution of issues that must be addressed in order, such as those of the VIG supply, indemnification, liability, etc. These could be addressed by the oversight group.
- There should be sufficient VIG to cover 5-7 million vaccinees, based on past usage. So, while that should not delay activity, other factors could (e.g., IRB issues). And, while

certain hospitals may be designated as smallpox hospitals, like it or not, in an epidemic all hospitals will be involved. So, one recommendation might be for hospitals to expect to receive patients, identify those who might be in contact with patients, and recommend that they be vaccinated. But the patients of most concern are those with the faster developing hemorrhagic smallpox, who, if not recognized on admission, might spread the disease in ICUs, EDs, etc.

- *Expansion of recommendation to include more hospital workers* was discussed by the working group. They anticipated, and think that the state plans include, that every healthcare facility have a plan to address the unexpected case (e.g., have appropriate pre-designated facilities to which patients would be referred for care). Hospital teams and out-of-hospital teams should be plan components, coordinated through the local public health agencies. If the problem is of a larger scale, the plan can designate other staff and hospitals. But once a single case is identified, a re-review of all staff immunization issues will be necessary. What is sure is that pre-vaccinated staff will be needed to address the first cases.
- The state plan should ensure that all ages are included, especially since few hospitals have a pediatric expertise. In fact, this recommendation should emphasize that everything, including federal action, relates to the state plan, which should be flexible and ensure that the necessary connections to other relevant groups and agencies have been made (e.g., with DVA and IHS for their special populations).
- *But the federal agencies cannot come in until invited by the state. Once in, who runs it?* The states need to think like an emergency response staffer. Emergency response plans are triggered by a smallpox case. There are designated statutory procedures to contact the federal agencies, which flow through the state's emergency management authority, which in turn feeds up to FEMA. That procedure dictates who is in charge. This would be a generic emergency category that happens to apply to public health.
- These issues present an opportunity to educate the public about public health, involving in this case a huge public relations issue. Explanation will be needed of the extent of the discussions leading to this recommendation, by the ACIP, by forums around the country, etc. This will help prevent panic or unease about what ACIP is about to do and avoid undermining the use of routinely recommended vaccines and those for adults. The letter of transmittal to the CDC and the Secretary should note that this public relations campaign will take time and resources to ensure the public's understanding. The importance of education and communication should also be stated right in the document.
- There is no mention yet of non-medical personnel such as FBI and other agency teams. However, all those who could be mentioned could be subsumed under the federal response team, and "security personnel" could include such agencies as FBI.
- Soften the text saying that smallpox vaccine "often" causes adverse effects in contacts to "sometimes" or "occasionally" to infer that this is not the rule (page 4).
- *Will the oversight include assurance that the state response teams are adequate?* The previous week, a CDC plan was drafted for an Oversight Board. But this was inappropriate to advance to the DHHS until the ACIP decided if it wished to expand the June 2001 recommendations. CDC supports such a board, but also wishes to consult

other interested agencies to obtain their buy-in. The latter also can be obtained through the bioterrorism cooperative agreements, which require preparedness plans.

- The perception that this will only happen if the federal government drives the states to effect this should not be encouraged. The ultimate responsibility for preparing for smallpox and implementing the plan lies with the states, which also will welcome any help. Oversight is wise and necessary, and the funding mechanism can arrange that, but the most important review of whether the state is ready is that of the state health officer and governor.

Vaccine Supply/Issues

Td: Dr. Philip Hosbach, of Aventis Pasteur, expressed AvP's appreciation of CDC's and the market's patience during the period of shortage. He reported sufficient tetanus vaccine production for emergency use (floods, military deployments). The lot production now allows routine Td use in all physician practices. The NIP's understanding is that there will be some improvement in the Td and DTaP vaccines supply, and hopes the other vaccine shortages to improve as well. An *MMWR* announcement will be published to this effect. And, with licensure of the second DTaP, AvP expects to supply >50% of the marketplace by the end of the year, bringing that shortage to an end.

MMR/varicella: Dr. Wharton stated that no information received yet suggests a change to the recommendations on MMR and varicella, but the ACIP will be advised when that occurs. The interim recommendations may be changed. The ACIP agreed, to an NIP request to publish in the *MMWR* a reversion to the original recommendations for MMR and varicella on the ACIP's behalf, and others as the supply situation changes.

Pneumococcal conjugate. Dr. Paradiso reported no resolution of the PCV supply shortage. Shortages persisted in the last two months, but a good bit of vaccine is being released this month. The company is trying hard to bring Prevnar® production up to demand. Dr. Abramson suggested NIP's consideration of: 1) a survey to determine the status of PCV use (i.e.,how many are using four doses); and 2) a campaign to emphasize not to administer the fourth dose. He commented that a tremendous maldistribution seems to persist. Dr. Modlin noted the need, before the next meeting, to address the issue of communications issues around the use of PCV. It is not certain that the ACIP recommendation has been adequately re-emphasized. A boxed *MMWR* notice may be called for.

General vaccine issues

NVAC: Dr. Peter reported on the NVAC's discussions of and impending statement on the vaccine supply, and strategies considered by NVAC's Vaccine Supply Working Group and a workshop held in February 2002. A report will be submitted to the Assistant Secretary shortly, and will be shared with the ACIP subsequently. One point made about immediate solutions is the need for a better funded stockpile, as well as discussion of financial incentives to support vaccine production. There was little interest in a national vaccine authority for childhood vaccines, but the concept of better prioritization for national vaccine issues was of interest, a mechanism for

which already exists in the NVPO.

Cold chain issues. Dr. Wharton reported an intended discussion at this meeting, before the DHHS request led to an agenda change, about vaccine stored at too-low temperatures. State health departments have asked NIP to look into this issue, which affects large numbers of children. An ACIP working group was requested to work with NIP to investigate and determine an appropriate response by state health departments. Dr. Modlin assigned this to the General Recommendations Working Group, which Dr. Tompkins chairs.

Influenza Statement

Dr. Word introduced several presentations on influenza immunization: 1) an easily corrected discrepancy noted after publication of the most recent recommendation; 2) an update on last season's influenza activity and the influenza activity agenda for this October's ACIP meeting; 3) an update on concerns about how families will pay for the shots discussed by last February's ACIP recommendation to encourage influenza immunization of small healthy children; 4) and information on CDC, AAP and AAFP activities to educate physicians and families about this recommendation (published in April) during this transition period.

Erratum publication. Dr. Carolyn Bridges reported that the influenza recommendation published in February had an inconsistency in the recommended timing of vaccination for target groups. One was to vaccinate high-risk persons and health care workers in October; and another recommended mass vaccination and large vaccination clinics to begin in mid-October and later. Household contacts were included in the latter but not the first group. The manufacturers' estimated cumulative production this year, of 92-97 million doses, is also substantially higher than that released in the past. To correct that inconsistency and in anticipation of the vaccine supply, an erratum will be published in two weeks. It will specify vaccination of the following groups to begin in October: persons at increased risk of influenza-related complications (to include healthy children aged 6-23 months), health care workers, household contacts of persons at increased risk of influenza, and contacts of persons aged <6 months who are not eligible for vaccine, as well as children aged 6 months-9 years receiving the vaccine for the first time.

The Committee had no questions or comments on that erratum.

Update on 2001 influenza/2002 plans. Dr. Keiji Fukuda reported a mild to moderate 2001 influenza season, which peaked in late February. Influenza A, H3N2 predominated. The H1N2 virus strains were identified in several states and countries worldwide. Since these are reassorted viruses containing current H1 and current N2 determinants, they posed no pandemic threat. Substantial B activity of two lineages was seen toward the end of the season, primarily the B/Yamagata-like and B/Victoria-like viruses. The upcoming season's vaccine will contain both the B/Yamagata and B/Victoria-like viruses. Dr. Fukuda shared charts of the strain circulation and the mortality/morbidity curves seen to date. The states should be aware that the B viruses peaked later in the season (even into June), and could still be circulating.

The October 2002 meeting agenda will devote increased time devoted to influenza, in order to

relieve the pressures of addressing all related issues at the one (February) meeting and to allow more time to prepare and produce an ACIP influenza control and prevention document. The issues likely to be raised in October are the 2003 strain recommendations, pediatric-related issues (vaccination encouragement and recommendations), and perhaps recommendations for the use of live attenuated influenza vaccine in October.

VFC coverage of influenza vaccination for children. Mr. Jim Singleton recalled ACIP's encouragement in February of influenza vaccination of children aged 6-23 months and of the contacts of children aged <2 years. Asking for vote to add these groups to eligibility for the VFC program, he reviewed the proposed changes and their rationale:

- Addition to eligible groups: Children aged 6 through 23 months. Rationale: children aged <2 years are at increased risk for influenza-related hospitalization and those aged <6 months are not eligible for influenza vaccination.
- Addition of children and adolescents aged 2 through 18 years who are household contacts of children aged <2 years." Rationale: Vaccination of children's household contacts may reduce the likelihood of influenza infection. Household contacts of persons in other high-risk groups (e.g., persons aged 17 to 65, transplant recipients, etc.) were already included.
- Minor changes were made to the dosage and interval schedule.

ACIP has encouraged vaccination of these groups, and a full recommendation could be issued by 2003-2005. However, reimbursement is a key concern of the ACIP as well as the AAP and AAFP. The addition of pneumococcal conjugate (PCV7) to the pediatric schedule of vaccines that "should be considered" for all children aged 24-59 months, provides a precedent to make this an eligible vaccination of the VFC. Eligible VFC groups include all infants and children aged 6 weeks to 59 months.

Vaccination schedule changes include to:

- To add "inactivated influenza vaccine" to the schedule title.
- Delete the split- versus whole-virus column (whole-virus vaccine is not available in the U.S.).
- Consolidate the age groups to 6 months to 8 years and >8 years.
- Add a footnote about Fluvirin™ as approved for use in persons aged ≥4 years.
- Changes to dosage intervals also added "influenza, inactivated" and a footnote to indicate that the Fluvirin™ purified surface antigen vaccine (Evans Vaccines, Ltd.) is approved for use only among persons aged ≥4 years.

Supporting data were supplied. A comparison was done of children for whom vaccination is currently "recommended" to the number involved by adding children aged <2 years to the high-risk group. The number of high-risk children under the current recommendation would rise from 8.05 to 13.69 million; those living with a high-risk person would rise from 24.53 to 27.24 million, and those in neither group would drop from 42.18 to 33.83 million.

These population numbers were then converted into those who are VFC eligible. Children now covered as at high risk would rise from 3.69 million to 7.01 million; those living with a high-risk person would rise from 11.38 million to 12.34 million; and healthy children in neither category would drop from 19.6 million to 15.32 million.

Cost estimates were based on several assumptions:

- Influenza vaccine costs $5.525 /dose for children aged ≥3 years, and half that for those aged <3 years.
- Two doses will be required for children aged <9 years receiving their first influenza vaccination.
- The distribution of public sector vaccine purchase was assumed to be the same as for MMR: for children aged 6-11 months, 63% funded by VFC, 11% by the 317 program, and 5% by the state; for children aged 12-23 months, 56% by the VFC, 11% and 6% by the 317 program and state, respectively; and for those aged 2-18 years, 45% by VFC and again 11% and 6% by 317 and state funding.
- The costs not included were for program infrastructure, the vaccine administration fee, and the vaccine wastage at the provider level (i.e., how many doses are actually delivered from a 10-dose vial).

Vaccine coverage scenarios outlined assumed an increase from 1% of 6-23 month-olds vaccinated to 20% in year 1 and an eventual steady rate of 80%; a 10% baseline for 2-18 years olds at high risk rising to 15% in year one and an eventual 60% steady state; and for those aged 2-18 years living with high risk persons, 1% coverage rising to 5% in year one and then to a 30% steady state.

In 2001, 607,000 influenza vaccine doses were purchased for the VFC. Assuming all doses are delivered to high-risk persons (3.69 million children), vaccine coverage would range from 8% to 16% (depending on how many children received one or two doses). Coverage, when adding in household contacts, would be <4% among the children eligible for the vaccine under the VFC, demonstrating the low current utilization of VFC for influenza vaccination.

Costs were summarized for the age groups for the VFC and 317 programs, state and total public costs. In terms of baseline, first year, and steady state, the costs for VFC in millions of dollars rose from $3.86 to $11.54, to $44.08, respectively; those for the 317 program rose from $0.95 to $2.56 to $10.12; and those for states, $0.55 to $1.42 to $5.44. The total public cost began at a $5.36 baseline and rose to $15.52 at the first year, before reaching a steady state of $59.64.

Discussion included:

- The table of the recommended inactivated influenza vaccine schedule references dose ranges (6-8 months, 6 months-8 years, and older). A smaller dose is given to those aged 6 months-8 years old. To avoid dosing errors, insert a footnote to emphasize that fact.
- *Please comment on the Guillian Barre Syndrome (GBS) issue as an adult or pediatric problem, and on the lack of association between the nasal influenza vaccine used in the*

U.S. versus the Swiss vaccine, and Bell's Palsy. Dr. Robert Chen reported GBS as an adult problem in the developed world, but a pediatric one in the developing world. The ecology of the developing child is very different than an adult's, particularly in the gut, something not considered with the rotavirus vaccine. Regarding Bell's palsy, the Swiss company that introduced a new intranasal influenza vaccine to their market stopped distribution when research showed a strong association with Bell's palsy. They will not reintroduce it. GBS cases in children have been reported after influenza vaccination, but those studies did not include children. The VAERS data review done last year uncovered five validated reports of this, which did not prompt further causality assessment (~1 each season could represent a background rate), but that was also in the period before expanded recommendations. It remains unknown if influenza vaccination is relevant to GBS in children.

- *How is the phrase "living in the household with" to be interpreted?* It infers those at close contact, whether or not living in the house (e.g., a frequently-babysitting grandparent who has close contact, or healthcare workers, as opposed to such casual contacts as store clerks). It was suggested, under eligible groups, 1) to include in the eligible groups "children and adolescents aged 2-18 years who are household contacts," as opposed to household "members," and 2) to make the terminology consistent (i.e., as opposed to currently interchangeable terms of "household members [and in the next sentence] household contacts and out-of-home caregivers.)" The April statement was similarly inconsistent. This will be in the *MMWR* article as well.

Vote. Dr. Zimmerman **moved to adopt this statement with the changes suggested from "household members" to "contacts.** The motion was seconded by Dr. Levin.

Conflicts with Wyeth, Aventis Pasteur or Evans affected only Dr. Rennels.

In favor:	Smith, Birkhead, Offit, Word, DeSeda, Levin, Brooks, Tompkins, Zimmerman, Hanson, Modlin.
Opposed:	None
Abstained:	Rennels

The **vote passed.** Subsequent to the ACIP meeting, an effective date was added to the VFC resolution to clarify the ACIP's intention that implementation would begin with the 2003-2004 influenza season: "March 1, 2003 for vaccine to be administered in the 2003-2004 and subsequent influenza vaccination seasons."

Implementation issues were outlined by Dr. Lance Rodewald. .

The programmatic implications include:

- Funding: This justifies the VFC funding request, helps identify the need for 317 funds; and helps states determine the need for state funds.
- Contracting: Resolution depends on the negotiation of a contract, but this signals

government interest. The contracting processes would be for the 2003-04 season.

- Implications to the Vaccine Injury Compensation Program are independent of a VFC resolution.

Challenges include:

- A practical lead time of <1 year. The federal contract interacts with the private suppliers. Almost all the influenza vaccine supply is in the private sector and vaccine is "booked" early in the calendar year since the vaccine delays.
- Therefore, projection of vaccine use needs to be accurate. Overestimates waste vaccine and money. States will be responsible for 45,000 individual estimates of vaccine need for the coming year (the number of VFC providers in the U.S.)
- Education of VFC providers will be needed. Ideally, this will be a collaborative effort with national organizations.

Challenges to the health care system include:

- Private insurance coverage rates for influenza vaccination are unknown.
- Immunization providers will want to avoid a two-tiered system. The public sector is currently ahead of the private sector in implementation, but vaccination may depend on the payment source. In addition, there is the challenge of high-risk patient identification, regardless of the VFC resolution, which will require active intervention in the physician's office.

Finally, this resolution provides opportunities:

- It backs the ACIP's encouragement of vaccination of young children against influenza with funding for a substantial pediatric segment.
- It may improve vaccination of those at high risk through the education promotion of the VFC program.
- It allows a "ramp-up" of this vaccine toward more aggressive influenza vaccination of children.
- And finally, it helps to provide a direct benefit for vulnerable children.

Discussion included:

- The desire was expressed to make this decision at the October meeting to move toward a recommendation for 2003 rather than 2004. This will allow the harmonized schedule to reflect that rather than having a footnote. This is now possible, since the issues of vaccine supply are solved; payment was solved with the VFC vote; and education is ongoing and planned. Dr. Modlin asked the Influenza Workgroup to take that under advisement with the Influenza Branch.
- In response to a question, Dr. Hosbach reported that AvP is working on using an alternative preservative to thimerosal in the influenza vaccine, but its effectiveness remains unknown, especially to avoid bacterial contamination of the egg-based protein vaccine. They also are working with the FDA on a reduced-thimerosal-containing influenza vaccine which may or may not be approved by FDA for this influenza season.

If approved, a limited number of doses could be released. However, the process reduces production capacity because repeated filtration to remove thimerosal also removes antigen. Accurate forecasting of this product's market will be necessary. Thimerosal remains the most historically dependable preservative. Clinical trials of the new preservative will probably be required.

Organizational Follow-Up to Influenza Recommendations

AAP. Dr. Peggy Rennels outlined the AAP's activities to support the ACIP influenza recommendations. It was published in the *AAP News,* posted on the AAP members-only network and included in the AAP's May media mailing. The technical report and recommendations were written and approved by the three AAP stakeholder committees and was now before the Pediatric Board. After their approval, it will be published in *Pediatrics*. The VFC vote will be publicized to the members, and the multiple lectures planned will include this recommendation. Dr. France reported that AAHP intends to convey to its members that this encouragement recommendation is a test trial of a recommendation. He hoped that the members will pick up that coverage even before the full recommendation.

AAFP. Dr. Martin Mahoney outlined initiatives by the American Academy of Family Practitioners (AAFP) to fully implement influenza vaccination of children at 6-23 months of age. They will incorporate this recommendation in their normal communication channels. These include posting information on their Website, distributing printed materials and publications, publication of the recommendation in their journal, *The American Family Physician* (a 2003 supplement on this recommendation is planned) and their semi-weekly e-mailed *FP Report* to ~25,000 members. The CME sessions at their our annual scientific assembly will update on immunization practices and policies. These will also be followed up upon at the state level CME sessions and in the state chapter newsletters. Affiliated organizations such as the Society of Teachers of Family Medicine offer expanded educational outreach, as well as the Website www.immunizationed.org, which also offers Power Point presentations and lectures.

CDC. Dr. Jerri Pickett updated the Committee on the CDC's activities related to the pediatric timing recommendations. The CDC Office of Communications will expand their traditional adult immunization focus to the new timing recommendations for healthy children aged 6-23 months and those aged 6 months to <9 years receiving vaccine for the first time. They will also conduct formative research this summer with pediatricians and with parents to explore their knowledge, attitudes, beliefs, and perceptions, particularly about immunization activities for children so aged. The resulting data will be used to develop concepts, messages and materials targeted to this audience, to be produced in English and Spanish. Dissemination of this information with partners is being explored, as are physician education campaigns.

Childhood Harmonized Schedule

Dr. Gregory Wallace, of the NIP, presented the proposed changes in the childhood harmonized schedule for provisional approval. The changes, which were redlined, 1) clarify the number of hep B doses in the series and the recommendation for serology testing in infants born to hepatitis

surface antigen-positive mothers; 2, revised the influenza footnote to incorporate the February 2002 recommendations for children aged 6-23 months old, with an updated *MMWR* reference; and 3) extend the Td bar for the adolescent booster back to 18 years of age to reflect the easing Td shortage, and replace the word "supply" with "shortages" to reflect the availability of that information on the NIP Website.

Dr. Modlin asked for comments and/or the Committee's provisional approval of the schedule, upon which it will be sent to the AAP and AAFP partners.

Discussion included:

- With Dr. Gary Freed's group at the University of Michigan, focus groups will explore how well this schedule is received by a range of providers (physicians, nurses, and other vaccine providers). The focus groups will evaluate the catch-up schedule as well. Among the questions for this schedule is how to alter the footnotes, which require a tinier font each year. Prioritization of what goes into a footnote is also needed; for example, the serologic testing of antigen positive mothers has been true for 6 years and may not require repeating. Some footnotes could probably be dropped, such as that noting the U.S.' an all-IPV schedule).
- Discussion of the 13-18 year-old bar was requested. As more vaccinations for adolescents are pursued (e.g, acellular pertussis and papilloma vaccines on the horizon, hep B for those not previously vaccinated, etc.), the Committee may wish to consider a focus on an "adolescent vaccination date" and modify this schedule accordingly.
- The AAP still hears of much confusion with the hep B schedule; many mistakes seem to be made in the first three initial doses. The focus groups should specifically be asked whether the message is being conveyed about hep B.
- The AAFP, subject to a few adjustments, supports this schedule.
- Dr. Wharton asked if the second half of the Td bar should be cross hatched as a catch-up bar for this year only, in view of the growing vaccine supply. However, that could apply to several other vaccines as well, and since the shortages seem to be in constant flux, keeping up annually might cause even more confusion.
- Dr. Wharton was comfortable with the Committee's approval, with the understanding that there may be minor changes, but major changes later in the year would be difficult to implement in view of the AAP/AAFP's required review.

Catch-up Schedule. Dr. Wallace showed two formats for the catch-up schedules for children age 4 months-6 years, and for children age 7-18 years. Version A was organized by vaccine type and Version B was organized by number of doses. As mentioned, the NIP will conduct focus groups of vaccine providers on both the catch-up and harmonized schedules, working with the University of Michigan. They will focus on the utility and format of the information provided, and suggestions to make them more user-friendly. They will also evaluate the clarity of the hep B schedule and the Hib and PCV schedules. Information from the focus groups will be available for the October meeting. More formal surveys on the utility of both schedules will be conducted subsequently.

Dr. Modlin asked the Committee to review the schedules and to provide feedback to Dr. Wallace in the next 3-4 weeks, if possible. Initial response included comments of a preference for version A, which seemed to flow better. The focus groups' input will be brought back to this Committee.

Vote on the DHHS Questions

After lunch, the members reconvened to review the revised draft recommendations on the use of smallpox vaccine. Dr. Kuritsky read through them, which incorporated the comments of the morning's discussions. The revised draft recommendation document is attached to this report. *Discussion* included:

- This draft dropped the guidance to establish one response team per million population.
- The text on "nurse vaccinators" should be dropped; insert instead, "doctors, nurses and other trained vaccinators."
- Reference the prior experience on which the Committee is relying.
- On the page 4, last paragraph, text that vaccinia virus is a live virus vaccine that can be transmitted person-to person: Include that "adverse effects may occur as well in vaccinees," or "which occur in individuals being vaccinated and can also occur in contacts."
- Change from "adverse effect" to "known reaction," except in the last paragraph's reference to surveillance of adverse events.
- Be consistent in referring to "adverse effect," "adverse reaction," or just use "smallpox vaccine complications." In addition, be consistent in calling it "smallpox vaccine," or "vaccinia vaccine." The compromise agreed to was "smallpox 'vaccinia' vaccine."
- There was general agreement to the following, with probable ensuing word-smithing: "Smallpox 'vaccinia' vaccine is a live virus vaccine that can cause adverse reactions in vaccinees and can be transmitted from person to person, which sometimes results in adverse reactions which also occur in the contacts of vaccinated persons."
- On page 3 specify that there is enough VIG to treat adverse events "...available under treatment IND," because the amount available is probably double the number that could be used under emergency IND.
- It was suggested to add, at the beginning of the surveillance section, the clinical case definition, but this will be done when the full statement is rewritten.
- Dr. Smith stated that ASTHO and other organizations will continue to work to draw up implementation guidelines.

Dr. Modlin summarized the changes suggested:

Page	Edits
3, last ¶	Add enough VIG available "... under treatment IND"
4, last ¶	Sentence 2, "Smallpox vaccine is a live virus vaccine that can cause adverse reactions in vaccinees and can be transmitted from person-to-person, and sometimes results in adverse reactions which also occur in the contacts of

	vaccinated persons."
All	Ensure consistency in how the vaccine is labeled; in the text and title, use "smallpox (vaccinia) vaccine."
5	Change "Nurse vaccinators" to: "diagnostic laboratory scientists, nurses, vaccinators, ..."

Vote: Dr. Tompkins **moved to adopt the supplement to the smallpox (vaccinia) vaccine statement**, and Dr. Rennels seconded the motion.

Conflicts:	Baxter, Acambis, Chesapeake Biologicals Laboratories. No members were in conflict.
In favor:	Modlin, Smith, Birkhead, Offit, Word, DeSeda, Levin, Brooks, Tompkins, Rennels, Zimmerman, Hanson
Opposed:	None
Abstained:	None

The motion **passed unanimously.**

Dr. Modlin thanked the staff for the immense amount of work required to bring this to the Committee at this meeting. He noted, though, that the Committee's work was just beginning, with much left to do before November. Dr. Snider thanked Dr. Modlin and the ACIP and the working group members for their work. The next steps are to deliver this recommendation to CDC, which will then deliver it to the department, and then proceed. He recognized the great amount of work and time that this has taken, and expressed his pride to be associated with a such Committee.

With no further comment, the meeting adjourned at 11:26 a.m.

I hereby confirm that these Minutes are accurate to the best of my knowledge.

_____

John Modlin, M.D., Chair

_____

Date

ATTACHMENT: Progression of Smallpox Disease